MOUNT SINAI
GUSTAVE L.
AND
JANET W.
LEVY
LIBRARY

MOUNT SINAI
GUSTAVE L.
AND
JANET W.
LEVY
LIBRARY

THE MOUNT SINAI JOURNAL OF MEDICINE

OF THE CITY UNIVERSITY OF NEW YORK

VOLUME 64 NUMBER 1 JANUARY 1997

CONTENTS

GRAND ROUNDS

Multisystem Granulomatous Disorders *Geraint James* 1

ORIGINAL ARTICLES

The Ethics of Managed Care *Fred Rosner for the Committee on Bioethical Issues of the Medical Society of the State of New York* 8

The Role of Sex Steroids in the Pathogenesis and Maintenance of Benign Prostatic Hyperplasia *Alice C. Levine, Alexander Kirschenbaum, and J. Lester Gabrilove* 20

DERMATOLOGY NOTES

Sarcoidosis *Stephen Kurtin and Mark Lebwohl* 26

ABSTRACTS

Research in Medicine 1996 Mount Sinai School of Medicine 27

Information for Authors 69

continued inside

STATEN ISLAND UNIVERSITY HOSPITAL
Affiliated with The Mount Sinai Hospital and Mount Sinai School of Medicine

Veterans Affairs

THE MOUNT SINAI JOURNAL OF MEDICINE

The Mount Sinai Journal of Medicine is published by The Mount Sinai Medical Center of New York and has the following affiliates: Bronx Veterans Affairs Medical Center, New York; Elmhurst Hospital Center, Queens, NY; Queens Hospital Center, Queens, NY; and Staten Island University Hospital, Staten Island, NY.

Editor-in-Chief
Sherman Kupfer, M.D.

Editor Emeritus
Lester R. Tuchman, M.D.

Associate Editors
Harriet S. Gilbert, M.D.
Julius Wolf, M.D.

Administrative Assistant
Joseline Ilagan

Assistant Editor for Housestaff
Rochelle Waldman, M.D.
Michael E. Blam, M.D.

Assistant Production Assistant
Mel Meyer

Assistant Editors
David H. Bechhofer, Ph.D.
Constanin A. Bona, M.D., Ph.D.
Edward J. Bottone, Ph.D.
Lewis Burrows, M.D.
Christopher P. Cardozo, M.D.
Mark R. Chassin, M.D., MPH, MPP
Joseph S. Eisenman, Ph.D.
Richard A. Frieden, M.D.
Frederick Friedman, M.D.
Steven Fruchtman, M.D.
Paul L. Gilbert, M.D.
James H. Godbold, Ph.D.
Richard S. Haber, M.D.
Noam Harpaz, M.D.
Tomas Heimann, M.D.
Sheldon Jacobson, M.D.
Barry W. Jaffin, M.D.
Joseph L. Kannry, M.D.
Samuel Kenan, M.D.
Suzanne Carter Kramer, M.Sc.
Mark G. Lebwohl, M.D.
Zvi Lefkowitz, M.D.
Kenneth V. Lieberman, M.D.
Lynda R. Mandell, M.D., Ph.D.
Steven Markowitz, M.D.
Bernard Mehl, D.P.S.
Myron Miller, M.D.
Edward Raab, M.D.
Elliot J. Rayfield, M.D.
Allan Reed, M.D.
Clive Rosendorff, M.D., Ph.D.
Fred Rosner, M.D.
Allan E. Rubenstein, M.D.
David B. Sachar, M.D.
Henry Sacks, M.D.
Ira Sanders, M.D.
Martin H. Savitz, M.D.
Clyde B. Schechter, M.D.
Stuart C. Sealfon, M.D.
Michael Serby, M.D.
Phyllis Shaw, Ph.D.
Alex Stagnaro-Green, M.D.
Barry D. Stimmel, M.D.
Nelson Stone, M.D.
Max Sung, M.D.
Rein Tideiksaar, Ph.D.
Richard P. Wedeen, M.D.
Vincent B. Zaccardi, M.D., D.D.S.

Editorial Board
Barry S. Coller, M.D.
Barry Freedman, M.B.A.
Richard Gorlin, M.D.
Nathan Kase, M.D.
Panayotis G. Katsoyannis, Ph.D.
Charles K. McSherry, M.D.
Jack G. Rabinowitz, M.D.
John W. Rowe, M.D.
Alan L. Schiller, M.D.
Alan L. Silver, M.D.
Alvin S. Teirstein, M.D.
Rosalyn S. Yalow, Ph.D.

The Mount Sinai Journal of Medicine (ISSN No. 0027-2507; USPS 284-860) is published 6 times a year in January, March, May, September, October, and November in one indexed volume by The Mount Sinai Medical Center, Box 1094, One Gustave L. Levy Place, New York, NY 10029-6574. Subscription price: individuals (U.S. and Canada), $75 per year; libraries and institutions (U.S. and Canada), $115 per year; individuals (outside U.S. and Canada), $100 per year; libraries and institutions (outside U.S. and Canada), $140 per year. Single copies $20. New subscriptions begin with the first issue of the calendar year. Send notice of change of address 60 days before its effective date. Periodicals postage paid at New York, NY and at additional mailing offices. POSTMASTER: Send address changes to The Mount Sinai Journal of Medicine, Box 1094, One Gustave L. Levy Place, New York, NY 10029-6574. Telephone number (212) 241-6108; Fax (212) 722-6386. Copyright 1997 The Mount Sinai Hospital.

DISCLAIMER: The statement and opinions expressed in the *Journal* by authors and contributors are solely their own and not those of The Mount Sinai Medical Center or The Mount Sinai Journal of Medicine. All advertisements are expected to conform to ethical standards, and their appearance does not imply endorsement or approval by The Mount Sinai Medical Center and/or The Mount Sinai Journal of Medicine of the products with respect to effectiveness, quality, or safety. The Mount Sinai Medical Center and The Mount Sinai Journal of Medicine do not hold themselves responsible for statements made by the authors or contributors, and for any injury to persons or property which may have resulted from ideas, products, and services referred to in articles or advertisements.

COPYRIGHT: Material printed in the Journal is protected by copyright. In accord with U.S. Copyright law, no part of the Journal may be reproduced, displayed, or transmitted in any form, electronic or mechanical, including photocopying or by any information storage or retrieval system, without prior written permission to do so. Permission should be requested from The Editor. The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574.

THE
MOUNT SINAI JOURNAL
OF MEDICINE

Volume 64
Number 1
January 1997

CONTENTS

GRAND ROUNDS

Multisystem Granulomatous Disorders *Geraint James* 1

ORIGINAL ARTICLES

The Ethics of Managed Care *Fred Rosner for the Committee on Bioethical Issues of the Medical Society of the State of New York* 8

The Role of Sex Steroids in the Pathogenesis and Maintenance of Benign Prostatic Hyperplasia *Alice C. Levine, Alexander Kirschenbaum, and J. Lester Gabrilove* 20

DERMATOLOGY NOTES

Sarcoidosis *Stephen Kurtin and Mark Lebwohl* 26

ABSTRACTS

Research in Medicine 1996 Mount Sinai School of Medicine 27

Information for Authors 69

Digitized by the Internet Archive
in 2015

https://archive.org/details/mountsinaijourna6419moun

Grand Rounds

Multisystem Granulomatous Disorders

GERAINT JAMES, M.D., F.R.C.P., F.A.C.P.

THE TWO PRINCIPAL DEFENSE SYSTEMS of the body are cell-mediated immunity and humoral or circulating immunity. Let us think of the two pioneers who laid the foundation of these two systems for which they deservedly shared a Nobel Prize in 1908. Elie Metchnikoff (1845–1916) was born in Russia, educated at the Kharkkov University and in Germany, and became a professor of zoology in Odessa (1872) and then at the Pasteur Institute in Paris (1888). He was a biologist, playing around with starfish, and he loved macrophages, phagocytes, and phagocytosis. He inoculated rose thorns into clear starfish larva which were devoid of blood vessels and a nervous system but, nevertheless, produced phagocytic inflammation. These cells were the forerunners of the cells which are involved in phagocytosis, granuloma formation, and cellular immunity.

Paul Ehrlich (1854–1915) was born in Silesia, Germany, the son of an innkeeper. He was educated at Strassburg University, became a physician at Leipzig (1878), and worked at Berlin's Charité Hospital and the Frankfurt Institute for Experimental Therapy. Apart from his interest in arsenical Salvarsan 606, he laid the foundation for humoral or circulating immunity with his descriptions of antigens, globulin antibodies, and agglutinins. I hope that Mount Sinai commemorates their joint Nobel Prize of 1908 by holding an immunology update in 2008.

We have advanced since the days when we recognized the thymus-mediated T cell and its role in cellular immunity, and the association of the B cell of the bursa of Fabricius of Aquapedente with humoral immunity. Fabricius was the professor of anatomy in Padua in 1600. More recently, we have recognized subsets of T_h1 and T_h2 cells, each with its own different brands of cytokines.

T_h1 versus T_h2

The naive CD45 RA^+ cell progresses to a T_h0 cell that differentiates into a T_h1 or T_h2 cell with repeated antigenic stimulation. Each type provides a different profile of cytokines and pathogenesis, and differing disease processes. T_h1 cells are associated with activated macrophages and the cytokine cascade is interferon γ (INFγ), tumor necrosis factor (TNF), and interleukins 1 and 2 leading to granuloma formation. A granuloma is the hallmark of T_h1 cell inflammation. By contrast, T_h2 cells are associated with eosinophil and mast cell activation, and the cytokine cascade is of interleukins 4, 5, and 10. Various disorders are now increasingly recognized to be associated with a T_h1 or T_h2 participation (Table 1). Could it be that the cytokines associated with the one may down-regulate or interfere in some way with the pathogenesis of the other? The T_h1 versus T_h2 profile may be divisive. For instance, tuberculoid leprosy is associated with a T_h1 profile, and lepromatous leprosy has a T_h2 profile. Leishmaniasis may be T_h1 (cutaneous form) or T_h2 (visceral leishmaniasis). Primary biliary cirrhosis has not yet been categorized, although both types of profiles have their supporters. Perhaps there are two types of primary biliary cirrhosis, the one with hepatic and pulmonary granulomas bearing a T_h1 profile and a more eosinophilic type bearing a T_h2 profile.

It is possible that cross-regulating mechanisms allow a shift from a T_h1 to a T_h2 cytokine production profile during progression to acquired immunodeficiency syndrome (AIDS). Interleukins 1 and 2 are the main growth factors for T_h1 cells and interleukin 4 is the main growth factor

---

Adapted from the author's Grand Rounds presentation at the Mount Sinai School of Medicine, New York, NY, on May 2, 1995. Final revision received February 26, 1996. Address correspondence to Geraint James, M.D., Professor of Medicine, Royal Free Hospital School of Medicine, University of London, 149 Harley Street, London W1N 1HG, England.

TABLE 1
A Comparison of T_h1 and T_h2 Profiles

Feature	T_h1	T_h2
Associate activated cell type	Macrophage	Eosinophil Mast cell B cell
Stimulating antigen	Bacteria Mycobacteria Virus	Allergens Helminth
Effector response	Granuloma	Allergic inflammation Eosinophilia Bronchospasm Wheezing
Cytokine cascade	Interleukins 1/2 Interferon γ Tumour necrosis factor	Interleukins 4/5/10 Leukotriene Prostaglandin Platelet-activating factor
Growth factors Transforming Platelet	Lead to fibrosis	
Disorders	Sarcoidosis Insulin-dependent diabetes Reactive arthritis Lyme arthritis Hashimoto thyroiditis Crohn's disease Multiple sclerosis	Asthma Toxocara Hypereosinophilia Mycosis fungoides
Dermatitis	Nickel-induced	Atopic
Leprosy	Tuberculoid	Lepromatous
Leishmaniasis	Cutaneous	Visceral
Primary biliary cirrhosis	? +	? +
Skin tests for	Delayed type hypersensitivity	Allergy

for the T_h2 cells. Type 1 cytokines may suppress Type 2 cytokines and *vice versa*. This phenomenon may permit a change of course of some disorders such as AIDS and primary biliary cirrhosis. At the present time this is an oversimplification, because many other factors including genetic background, the type of antigenic challenge, age, sex, hormones, and constitution or terrain may be important influences. Various examples of T_h1-type granulomatous disorders can now be considered.

Sarcoidosis

A chronic type of sarcoidosis which presents with lupus pernio, the chilblain nose of sarcoidosis is demonstrated in Fig. 1. By looking at this patient's face, you can be certain that she has chronic fibrotic pulmonary sarcoidosis. This fibrosis will never disappear. Likewise, she may have bone cysts. It is a waste of time for physicians to obtain bone x-rays in patients with sarcoidosis, because they rarely find bone cysts. But if you are a dermatologist, you should always obtain x-rays of the bones because the yield is very high.

The foundation of sarcoidosis is the antigen-driven, cell-mediated immune response. The antigens may be exogenous or endogenous. If you are looking for sarcoidosis in the United States, you will see a high incidence in blacks. In London, it is seen in West Indians, in the Irish, and in the Scandinavians. You rarely see sarcoidosis in the Chinese, Greeks, and Cypriots. In sarcoidosis, a constitutional diathesis and a well-recognized human leukocyte antigen (HLA) type exists among certain ethnic groups.

The diathesis, or terrain, as the French call it, occurs in women in their 20s, pregnant or lactating, with certain HLA types especially when they encounter mycobacteria, pine pollen, peanut dust, or other etiologic agents. Only when those factors occur in the right diathesis will the syndrome emerge. On his deathbed, Louis Pasteur quoted Claude Bernard, his guru and counselor, "yes, Claude is right, the organism is nothing, the terrain is everything." Louis Pasteur, who spent a lifetime isolating organisms in the fermentation and milk industries, acknowledged that Claude was the one who was really right. Do not keep looking for the organism, keep looking for the terrain.

When we have diagnosed sarcoidosis, we are eager to know whether it is active or not, because we want to know whether we should treat it or not. Currently, sarcoid activity is suggested by certain tests. However, it is most important to develop tests to determine whether sarcoidosis

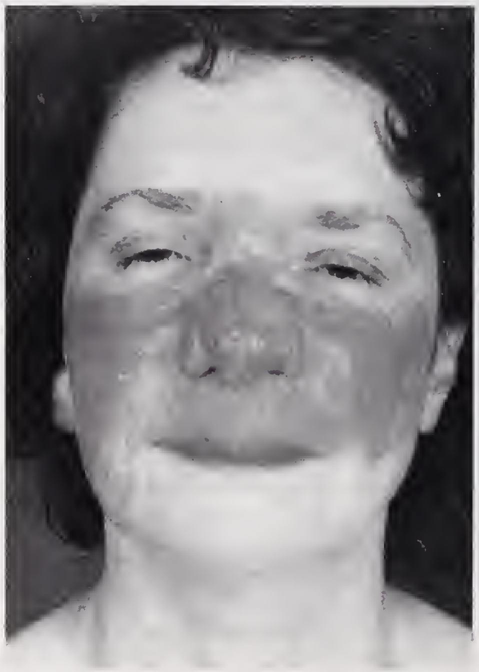


Fig. 1. Extensive lupus pernio in chronic sarcoidosis. (Reprinted with permission from James DG, Studdy PR. A colour atlas of respiratory diseases. London: Wolfe Medical Publications Ltd., 1981.)

will progress to fibrosis. Sarcoidosis would be an unimportant disease but for its propensity to cause fibrosis. A large body of work is in progress trying to isolate chemicals that may prevent fibrosis.

Kaposi Sarcoma

Kaposi sarcoma is another disease in which there is a lot of work concerning T_h1 versus T_h2 reaction. Kaposi was from Kaposva, a little place in Hungary. He married Martha, the daughter of the great von Hebra, the professor of dermatology in Vienna. Having married her, he eventually became chairman of dermatology in Vienna. Von Hebra's textbook of dermatology, which was used worldwide, became Kaposi's textbook of dermatology. On the open market now this three-volume textbook of Kaposi costs ten thousand dollars, and climbing, because of AIDS.

Wegener's Granulomatosis

I saw a 25-year-old nurse whose nose fell in (Fig. 2). You may be thinking of sarcoidosis, tuberculosis, leprosy, and so on. The referring letter said she had sarcoid tissue in the nose, ocular inflammation, and an abnormal chest x-ray (Fig. 3). But this constellation does not have to be sarcoidosis. We performed a C-ANCA test, which showed that she had Wegener's granulomatosis. Wegener was a good friend of mine. He was the German shotput champion in the 1930s. In 1937, he first described his granulomatosis. At that time, there was 100% mortality. Then came steroids and cyclophosphamide, and the prognosis improved. Before Wegener died, about 3 or 4 years ago at the age of 84, he told me that it was wonderful that C-ANCA had brought a quick method of early diagnosis. The Mayo Clinic has always believed that there is a bacterial background to Wegener's granulomatosis and have prescribed trimethoprim sulfamethoxazole. In fact, patients with Wegener's granulomatosis have a high incidence of residual staphylococcal infection in the nose and antibiotics might help. I perform cultures of the nose of all my patients with Wegener's.

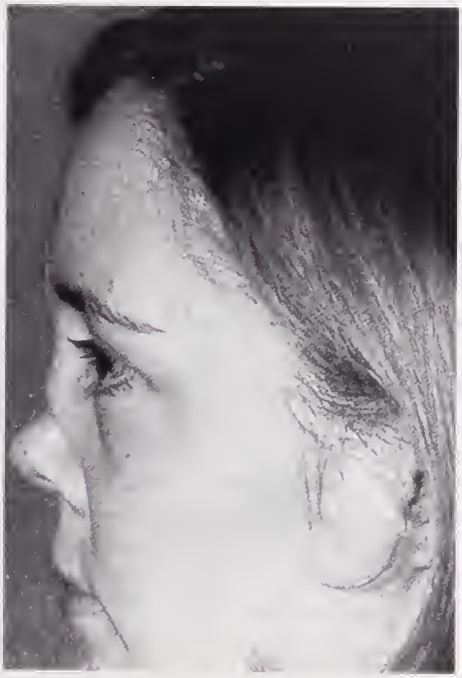


Fig. 2. Generalized Wegener's Granulomatosis. Destroyed nasal cartilage and saddle nose deformity are demonstrated. (Reprinted with permission from James DG, Studdy PR. A colour atlas of respiratory diseases. London: Wolfe Medical Publications Ltd., 1981.)

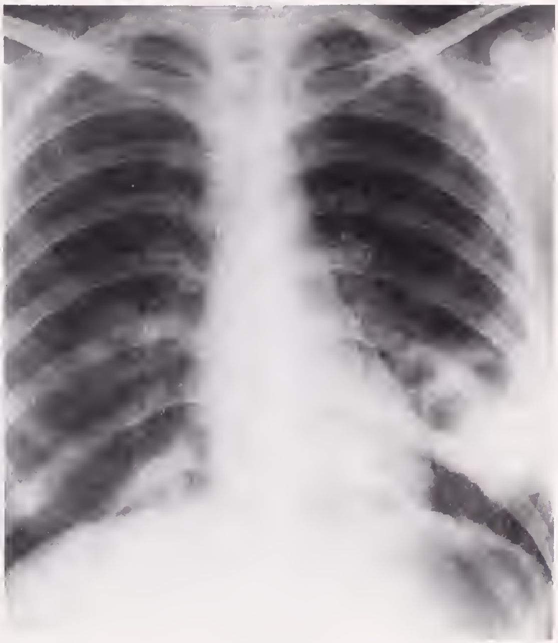


Fig. 3. Localized Wegener's Granulomatosis. Cavitation in left lung is evident. (Reprinted with permission from James DG, Studdy PR. A colour atlas of respiratory diseases. London: Wolfe Medical Publications Ltd., 1981.)

Langerhans' Granulomatosis

If you see young, heavy-smoking men whose lung biopsy shows sarcoid tissue and your endocrinologist says they have diabetes insipidus, it is predictable that many will call that sarcoidosis. If you wanted to throw a third feature into this group, they often have pneumothorax. This is not sarcoidosis; it is another mimic. It used to be called histiocytosis X, and now it is called Langerhans' histiocytosis. It is not surprising that these men have pneumothorax because they have many subpleural cysts. This disease is absolutely unrelated to sarcoidosis. The latest treatment now is leustatin, which is a purine analog. It is an antihistiocytic agent and supplements radiotherapy and combination chemotherapy. The patients are young men in their 20s with neutrophilia who are always heavy smokers. Langerhans (1847–1888) was given this eponym some 100 years after his death. He has earned eponyms for other things, Langerhans' cell, islets of Langerhans. But now, 100 years after his death, we have begun to use the term Langerhans' granulomatosis. He was the great professor of pathology in Freiberg. He was the Hans Popper of Germany. Like Hans Popper, he had a famous doctor father. He died of tuberculosis in Madeira.

Leprosy

I saw a patient who was in London on her honeymoon. I saw her because a biopsy showed sarcoid tissue. All that glitters is not sarcoid. This was tuberculoid leprosy. She was treated and did well. On the other hand, patients with lepromatous leprosy do not do as well. In fact, now that we give them interferon injections, they do better. You can convert them from lepromatous to tubercular leprosy. The World Health Organization (WHO) says we should eliminate leprosy by 2015. Bacille Calmette-Guérin and ofloxin, which is given free throughout Africa, and rifampicin, dapsone, and so on, are all being tried in an intensive effort to overcome the scourge of leprosy.

Hepatic Granuloma

The liver is another rich source of epithelioid cell granulomas (Table 2). Here is a 40-year-old woman with severe itching and perhaps a little jaundice caused by primary biliary cirrhosis. Two people are itching. She is itching, and some surgeon is itching to do a laparotomy, because that is the quickest way to make the diagnosis. In liver biopsies, sarcoidosis and primary biliary cirrhosis are often confused, but not in clinical practice (Fig. 4). The diagnosis can be made by conducting a mitochondrial antibody test and a Kveim-Siltzbach test (Table 3). It can be confusing if you see a pathology slide of a liver biopsy without the clinical picture.

TABLE 2
Causes of Hepatic Granulomas

1. Infections
   - Mycobacteria
     - Tuberculosis
     - Leprosy
     - Avium intracellulare
   - Bacteria
     - *Brucella*
     - *Francisella tularensis*
     - *Yersinia*
     - *Proprionibacterium*
     - *Pseudomonas pseudomallei* (melioidosis)
     - Whipple's disease
   - Spirochaeta
     - Bacille Calmette-Guérin vaccine
     - *Treponema*
   - Fungi
     - *Blastomyces*
     - *Coccidioides*
     - *Histoplasma*
     - *Cryptococcus*
   - Protozoa
     - *Leishmania*
     - *Toxoplasma*
   - Metazoa
     - *Schistosoma*
     - *Toxocara*
   - *Rickettsia*
     - Q fever
     - Boutonneuse fever
   - Viruses
     - Hepatitis C virus
     - Cytomegalovirus
2. Chemicals
   - Beryllium
   - Copper
   - Drugs
3. Immunological upset
   - Sarcoidosis
   - Crohn's disease
   - Ulcerative colitis
   - Primary biliary cirrhosis
   - Hypogammaglobulinemia
   - Systemic lupus erythematosus
   - Immune complexes
   - Hepatic granulomatous (granulomatous hepatitis)
   - AIDS
4. Enzyme defect
   - Chronic granulomatous disease of children
5. Neoplasia
   - Reticulosis
   - Carcinoma
6. Miscellaneous
   - Cholestasis
   - Polymyalgia rheumatica
7. Drugs

Crohn's Disease

A surgeon in London performed a biopsy of an ulcer of the penis which showed sarcoid tissue. The surgeon who did the biopsy asked "How often do you see sarcoidosis of the penis?" The answer was never. The more likely diagnosis is that of Crohn's Disease in which there may be granulomas from mouth to anus and paragenitally. If you do bronchial lavage with patients with Crohn's Disease, you will obtain cells such as macrophages and CD4+ lymphocytes, much like those seen in sarcoidosis.

Leishmaniasis

I am presenting the mimics to you because they are confusing. One such example is the skin granuloma in a Scottish soldier who fought in the Gulf War. When he returned home, a skin lesion was biopsied and reported as sarcoid tissue. He was treated for sarcoidosis, although these lesions were restricted to his legs. Because he is a Scot, he does not wear trousers, he wears a kilt. By wearing a kilt, desert sand flies had bitten him on his legs and he contracted leishmaniasis, T_h1 granulomatous leishmaniasis.

Lymphomatoid Granulomatosis

Hans Popper would be delighted to have seen this granulomatous vasculitis which married a T cell lymphoma (Fig. 5). These patients are men in their 40s with cavitating lung nodules (Fig. 6)

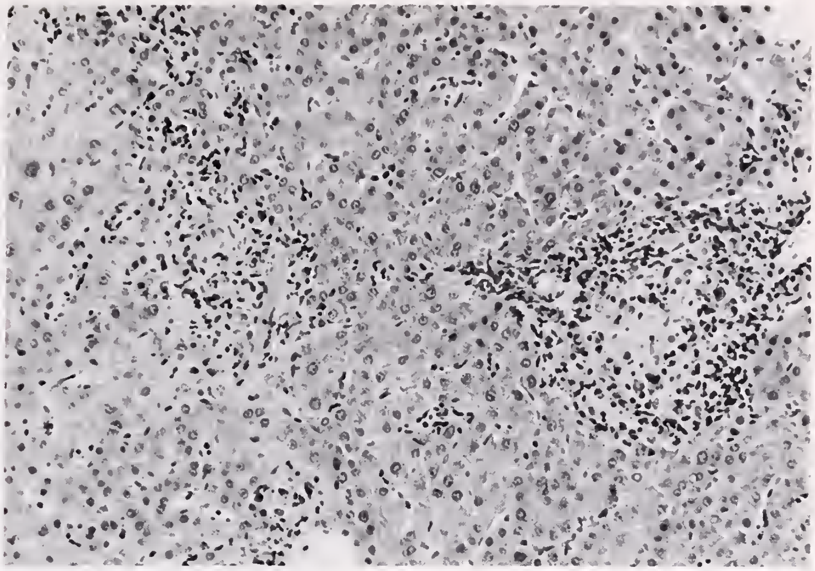


Fig. 4. Liver biopsy showing primary biliary cirrhosis (hematoxylin and eosin, ×40). The epithelioid macrophages are surrounded by lymphocytic and plasma cell infiltrate.

TABLE 3

Features Distinguishing Sarcoidosis from Primary Biliary Cirrhosis

Features	Sarcoidosis	Primary Biliary Cirrhosis
Sex F:M	Equal	8:1
Decade of onset	3, 4	5
Diagnosis over 40 years	Rare	Frequent
Erythema nodosum	Yes	No
Uveitis	Yes	No
Respiratory	Yes	No
Pruritus	No	Yes, eventually
Jaundice	No	Yes, late
Xanthomas	No	Yes, late
Clubbing	No	Yes
Hepatomegaly	Infrequent	Usually
Splenomegaly	Yes	Yes
Skin pigmentation	No	Yes
Steatorrhea	No	Yes, with jaundice
Bilateral hilar lymphadenopathy	Yes	No
Kveim-Siltzbach test	Positive in 80%	Always negative
Depression of delayed-type hypersensitivity	Yes	Yes
Circulating mitochondrial antibodies	No	Yes (in 99%)
Calcium metabolism	Hypercalcemia Vitamin D sensitivity	Hypocalcemia (steatorrhea)
Raised serum Alkaline phosphatase	Yes, minority	Yes, in most
Angiotensin-converting enzyme	Yes, in 60%	Yes, in 16%
Live granulomas	Yes	Yes
Corticosteroids	Helpful	Contraindicated
Vitamin D	Contraindicated	Helpful
Cholestyramine	Not necessary	Helpful
Prognosis	Very good	Variable

appearing exactly like Wegener's granulomatosis. They have skin lesions like lupus pernio. On some occasions, eye changes and paresis may be present. There is a high mortality. Remember that lymphomatoid granulomatosis may look like lupus pernio, but that the latter disorder is seen in women, the former in men. You need a good pathologist to tell this T_h1 granuloma from the others.

Miscellaneous Granulomatous Disorders

There is a miscellaneous group of granulomatous disorders. Some patients present with thick edematous lips, thick tongue, and thick gums, cervicofacial tissues and biopsies from each area show histological features similar to that seen in sarcoidosis. This is the Melkersson-Rosenthal's syndrome, which mimics sarcoidosis (Fig. 7). Egyptians, who paddled in the Nile once too often, may contract cell-mediated immune reaction to Bilharzia and biopsy will reveal another T_h1 granuloma, schistosomiasis. If you see granulomas in abdominal lymph nodes, think of helicobacter. If granulomas occur in axillary lymph nodes, think of cat scratch disease. If multiple lymph nodes are involved, it might be acquired toxoplasmosis.

Finally, I want you to help me with this last patient. He is a 36-year-old physician who developed fever, arthritis or polyarthralgia, and a bit of diarrhea. The hospital where he was admitted did every test under the sun and the only thing that

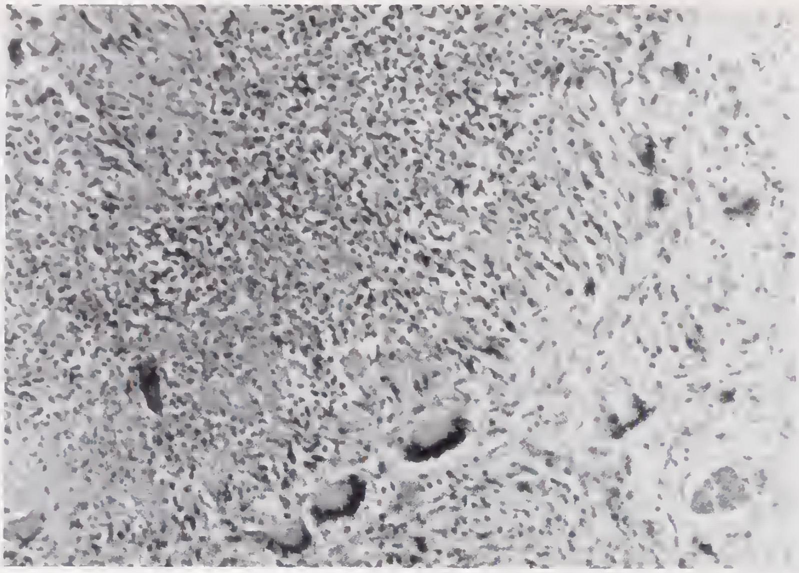


Fig. 5. Lymphomatoid granulomatosis (hematoxylin and eosin, ×40). This is a highly cellular atypical lymphoreticular infiltrate, rich in mitosis, which often invades and destroys blood vessels. (Reprinted with permission from James DG, Studdy PR. A colour atlas of respiratory diseases. London: Wolfe Medical Publications Ltd., 1981.)

was positive was granuloma in the liver biopsy. It was called sarcoidosis. This happens very often with localized granulomas in one organ system. However, when the findings are localized to one organ system, think of anything but sarcoidosis. They gave him steroids for a year, during which time he got worse. If you forget everything I have said about T_h1 and T_h2 cells, remember that if you give steroids to a patient with sarcoidosis he feels better and objectively gets better. But this patient, with diarrhea, developed steatorrhea, lost weight, and with prolonged administration of steroids he lost height. He became much worse. After 1 year, they said, we will do a proper laparotomy. They found granulomas everywhere in the peritoneum, in the liver, and in the intestines. Well, if you find granulomas in the intestine, you ought to think of tuberculosis. Even if the disease has been present for a year or more, you have to think of low-grade Hodgkin's disease. These are

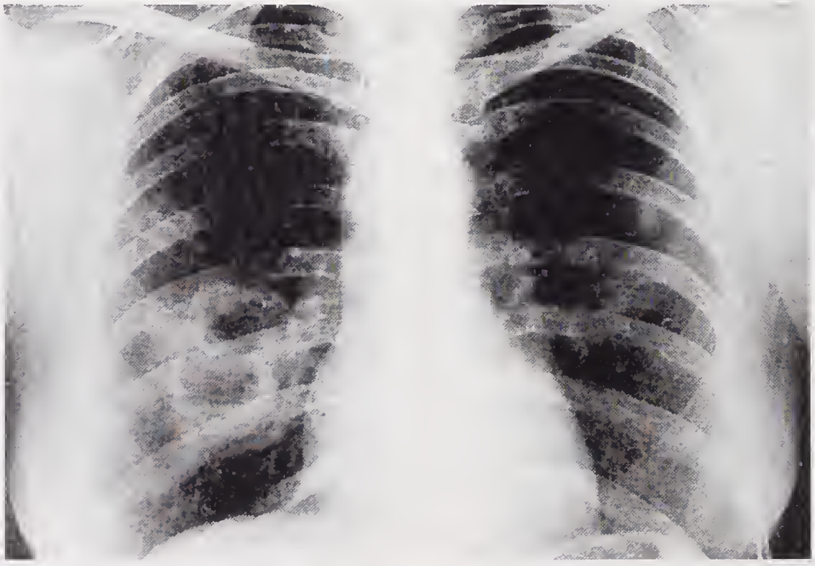


Fig. 6. Lymphomatoid granulomatosis. Bilateral opacities and cavitation are present in the right midzone. (Reprinted with permission from James DG, Studdy PR. A colour atlas of respiratory diseases. London: Wolfe Medical Publications Ltd., 1981.)

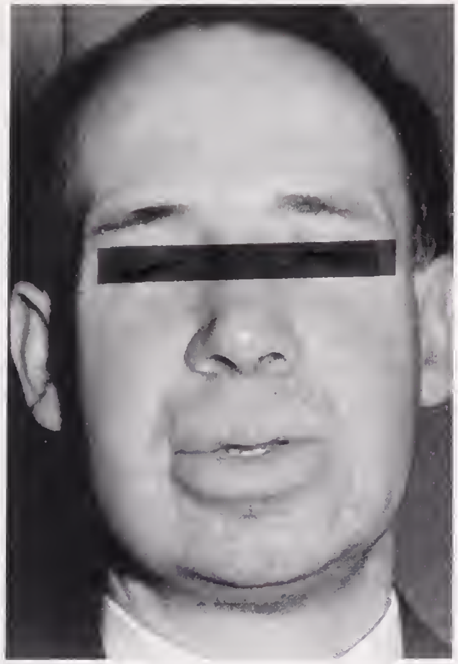


Fig. 7. The Melkersson-Rosenthal Syndrome. Circumscribed edema of the lips, periorbital tissues, and forehead is evident. (Reprinted with permission from James DG, Studdy PR. A colour atlas of respiratory diseases. London: Wolfe Medical Publications Ltd., 1981.)

TABLE 4

Differential Diagnosis of Sarcoidosis and Whipple's Disease

Feature	Sarcoidosis	Whipple's Disease
Other names		Lipophagic intestinal granulomatosis
Sex	Equal	Males predominantly
Decade	3 and 4	4–7
Nondeforming arthritis	Yes with erythema nodosum	Characteristic initial
Steatorrhea	No	Severe principal feature
Diarrhea	No	Yes
Weight loss	Infrequent	Frequent
Lymphadenopathy	27%	40%
Polyserositis	No	Yes
Periodic-acid Shiff stain of macrophages in lymph node	Negative	Positive
Duodenal biopsy	Normal	Periodic acid-Schiff staining macrophage Polymerase chain reaction defines Tropheryma
Electron microscopy	Negative	Tropheryma
Tropheryma in	No	Peripheral blood leucocyte
Treatment	Corticosteroids	Antibiotics

your alternatives to sarcoidosis. But you also have to do one other thing. You must do proper periodic acid-Schiff stains, and instantly you will recognize Whipple's disease. Whipple's disease is a great mimic of sarcoidosis, especially because of the fever and the polyarthralgia (Table 4). Whipple wrote one paper in 1908. Do you remember that year? 1908 was a great year. It was the year that Metchnikoff and Ehrlich shared the Nobel Prize. Whipple's paper described one patient who was a physician and a missionary, who presented with fever, polyarthralgia, and diarrhea. At the time Whipple was working at The Johns Hopkins Hospital and the paper appeared in *The Johns Hopkins Hospital Bulletin.* We now know the cause of Whipple's disease. You can make the diagnosis from a duodenal biopsy and by electron microscopy. Also, you can identify the organism from peripheral blood leukocytes by performing a polymerase chain reaction. When we gave our patient antibiotic therapy, and most any will do, he improved and went back to work.

Question from the audience: Do you use the Kveim test?

Dr. James: Oh, yes. In fact, I think I was the person who linked Kveim to Siltzbach. When I see articles in which it is called a Kveim test, I reject the article, because I do not think it was a good antigen until Siltzbach validated it. It is really like saying Kveim Mount Sinai. It is a good test with validated antigen. But there are some awful Kveim antigens around the world.

Question from the audience: You mentioned tuberculosis—what about the newer work showing polymerase chain reaction indicating tuberculosis DNA in patients with sarcoidosis?

Dr. James: Well, I do not believe it. These tests have shown mycobacteria residues. This is a long story going back to 1961. There has been a fierce tussle in Europe. The Germans and the French lined up against the Londoners. It is a whole story in itself. The latest is that we do not quite believe it.

Question from the audience: Do you believe that there is more than one cause for sarcoidosis?

Dr. James: That is correct. I think that there is a diathesis and then if a patient meets peanut dust in Richmond, Virginia, the peanut dust could spark it off as might other antigens in various parts of the world.

Dr. Alvin Teirstein: I think I should tell you that we have grown mycobacterial L forms from the blood of 19 of 20 patients with sarcoidosis. I do not think we have heard the end of the mycobacteria story. Gerry, thank you very much.

The Ethics of Managed Care

Fred Rosner, M.D., F.A.C.P.

Abstract

Ethical concerns relating to managed care discussed in this essay include incentives to underutilize services, delays in care, postponement of consultation or hospitalization, gatekeeping, patient satisfaction, physician satisfaction, and information disclosure. Because managed care is here to stay, physicians and patients must learn to understand it and develop methods to work with it, preserving the overriding principle that the physician's first obligation is to be the patient's advocate. Physicians must continue to practice good medicine, eliminate that which is unnecessary, and be conscious of the need to contain costs.

The need for health care reform in the United States is obvious. The costs of medical care continue to escalate despite utilization review, quality assurance, and the diagnostic-related group prospective payment system for hospital care. Large numbers of Americans are uninsured or underinsured. Inequities in physician reimbursement exist. Health services utilization and hence costs vary considerably in different geographic regions and the problem of malpractice litigation remains uncontrolled.

Enrollment in managed care plans has increased dramatically over the past decade and continues to grow as a cost containment strategy (1). Both government and the private sector believe that capitation payment for physicians is less expensive than fee-for-service medicine. Alternative systems for the provision of health care include: 1) the single-payer model of a national health plan (the Canadian system); 2) the "play or pay" approach in which employers are obligated to provide basic health care benefits for their employees and their dependents or pay a tax to finance a public program for the uninsured; 3) expansion of Medicare to all Americans; and 4) the Oregon-type initiative to ration very expensive medical services that benefit only a few patients to provide basic health care services for all citizens. Managed care as provided by health maintenance organizations (HMOs) and preferred-provider organizations (PPOs) may limit the patient's choice of physicians. Indemnification insurance plans offer a free choice of physicians, "but manage care by monitoring claims and denying or reducing payment for those deemed unjustified" (2). The various forms of managed care have been detailed by Iglehart (3).

In 1989, Enthoven and Kronick proposed a "Consumer-Choice Health Plan for the 1990s: Universal Health Insurance in a System Designed to Promote Quality and Economy" (4). Their strategy was based on managed competition in which collective agents called sponsors, such as the Health Care Financing Administration and large employers, contract with competing health plans and manage a process of informed cost-conscious consumer choice that rewards providers who deliver high-quality care economically. Enthoven and his colleagues reit-

---

Prepared as an educational and informational report by the Committee on Bioethical Issues of the Medical Society of the State of New York: Fred Rosner, M.D. (Chairman), Allen J. Bennett, M.D. (Vice Chairman), Jeffrey T. Berger, M.D., Anthony Buscaglia, M.D., Eric J. Cassell, M.D., Peter B. Farnsworth, M.D., Abraham L. Halpern, M.D., Pieter Kark, M.D., Allison B. Landolt, M.D., Laurence Loeb, M.D., Robert E. Lowenstein, M.D., Ph.D., Patricia J. Numann, M.D., Fernando V. Ona, M.D., Samuel Packer, M.D., Herman M. Risemberg, M.D., Peter Rogatz, M.D., Philip H. Sechzer, M.D.

Address correspondence to Fred Rosner, M.D., F.A.C.P., Mount Sinai Services at Queens Hospital Center, 82-68 164th Street, Jamaica, NY 11432.

erated their proposal on many occasions (5) and they became known as the Jackson Hole Group. This approach to health care reform was criticized as not being able to control health care expenditures and not ensuring access and quality (6). President Clinton's Health Security Act, proposed to Congress in September 1993, incorporated basic elements of this manged competition approach to health care.

Managed competition and managed care are distinct mechanisms of cost containment. Under managed competition, health care organizations are required to compete with each other for patients on the basis of both price charged and quality of service rendered, thus fusing the principles of managed care with those of the market to further control costs (7, 8).

Important questions are being asked about health care reform. Where are we and where should we be going? (9). How much will health care reform cost? (10). Would managed competition control costs? Could the Clinton health reform proposals be framed as a debate concerning moral issues such as universal access, reasonable equality of benefits, fairness of burdens, quality and efficiency of care, rationing, confidentiality of patient information, and so forth? (11). Fleischman (12) has stated that "Ethics is critical in framing the health care reform debate and in monitoring the outcome of the process. Although the present debate mainly focuses on pragmatic concerns in politics and economics, the proposed solutions will be acceptable only if the values reflected in the choices are reasonable and defensible."

This article discusses some of the ethical issues relating to managed care and critiques some of the current and proposed practices of this health care system which affect the patient, the physician, the managed care company, and society in general.

Health Care Reforms and Proposals

The Clinton Health Care Task Force assembled an Ethics Working Group in March 1993 to develop the ethical foundations for the Clinton administration's proposed health care system (13). These principles and values included the following: universal access to equal, comprehensive lifetime benefits; a financing system that fairly distributes the financial burden, wise allocation of resources; delivery of effective services and avoidance of ineffective ones; "a simply organized, efficiently managed system in which individual choice, personal responsibility, and professional integrity are all respected; and fair procedures for making decisions and resolving disputes" (14).

The Ethics Working Group recognized and illustrated numerous areas of potential conflict in the implementation of the moral ideals of justice, equality, and liberty with efficiency and the like. Pellegrino pointed out that the magnitude of the conflicts between a physician functioning under traditional fee for service and the same physician functioning under a managed care system was seriously underestimated (15).

No one disputes that ethical concerns are critical in the health care reform debate and in monitoring the outcome of whatever system is fully adopted. Unfortunately, the debate focuses mainly on pragmatic political concerns and economics. One of the most critical of concerns for physicians and patients is the maintenance of the patient-physician relationship which is threatened under managed care systems where physicians are asked to serve as "double agents weighing competing allegiances to patients' medical needs against the monetary costs to society" (16). The practice of medicine and the patient-physician relationship should not be part of a political agenda. Because most advocates of managed care and managed competition have business backgrounds rather than clinical experience, patients are viewed mainly as cost-conscious consumers and the patient-physician encounter as a market arrangement (17).

Lundberg (18) described an 11-point rating system for the various health reform proposals: 1) Does the proposal provide access to basic care for all; 2) produce real cost control; 3) promote continuing quality; 4) reduce administrative hassle and cost; 5) enhance disease prevention; 6) encourage primary care; 7) consider long-term care; 8) retain necessary patient autonomy; 9) retain necessary physician autonomy; 10) limit professional liability; and 11) possess staying power? Unfortunately, it is likely that this utopian grading system cannot be fully implemented. Lundberg supports the ethical principle of the greatest good for the greatest number.

Ethics of "Gatekeeping"

More than a decade ago, the gatekeeper concept became widely adopted as a method of cost containment. The primary physician who manages the patient's medical care is expected to control access to specialists and to expensive technology. The gatekeeper concept has been adopted by both prepaid group practice and individual practice association HMOs and is not tied to capitation payment.

Despite the potential of the gatekeeper plan to contain costs, several serious problems were identified as soon as experience with gatekeepers began. These problems include underutilization of services, the threat to free choice (Medicaid patients may have no choice at all), concern about restraint of trade by HMOs, the need for physician and/or patient incentives, the ability of primary care physicians to control use of medical care by serving as "policemen," the limited information on cost-effective medical practice, the selection or rejection of physicians by HMOs, and gatekeepers treating patients beyond their training or competency because of HMO constraints instead of timely referral or consultation (19).

The ethics of medical gatekeeping was addressed in detail in 1986 by Pellegrino who described three ways in which a physician can function as gatekeeper: one is morally mandatory, one is morally questionable, and one is morally indefensible (20). The first of these is traditional gatekeeping in which the physician recommends tests, treatments, and consultations that are appropriate, effective, and beneficial to the patient. According to Pellegrino, the physician should use "diagnostic elegance and therapeutic parsimony." This is the way to practice good medicine.

The morally questionable or negative form of gatekeeping is where the physician is pressured to restrict the use of tests and treatments, particularly those which are very expensive. One such pressure is the system of diagnosis related groups (DRGs) which assigns a fixed payment or number of days of hospitalization. If the number of days is exceeded, the hospital does not receive payment for the number of days which exceed the DRG allowance. In capitation payments, if the total cost of medical services exceeds the contracted amount, the provider bears the loss; if the costs are less, the provider makes a profit. Extra funds are not provided for sicker patients who may require longer hospitalizations. Financial incentives and disincentives to the physician replace quality of medical care. The main pressure point is at the level of the primary care physician who is the gatekeeper and has the greatest influence over access to expensive resources of technology and consultations.

The third form of medical gatekeeping which Pellegrino characterizes as morally indefensible is positive gatekeeping. Here the physician *increases* access to medical services in that he shares in the profit directly if he is an owner or investor in the service being provided. For those who can pay, the latest and most expensive diagnostic and therapeutic services are offered. The physician may be "rewarded by pay increases and advancement" in the HMO in which he is employed (20). Such positive gatekeeping is not unique to the managed care system. The same problem exists under a fee-for-service system where physicians may inappropriately overutilize services for financial gain. This practice, under any health care system, is morally indefensible.

The Patient-Physician Relationship

The traditional patient-physician trust relationship is threatened under managed care which creates conflicting loyalties for the physician who has to balance the interests of each patient against the interests of other patients and the financial interests of the managed care plan. Salaried physicians under managed care can be adversely affected if they "overutilize" services such as consultants and expensive tests. Physicians have been terminated from HMO for "overutilizing" services (21). Bonuses may be paid to physicians who "underutilize" services. Some managed care plans have practice guidelines which determine for a physician which services should be offered. Some managed care plans instruct physicians how to make allocation decisions. All these considerations that involve "bedside rationing" and which may include denial of a consultation or procedure that might benefit the patient conflict with the physician's traditional role as patient advocate (22). These considerations may also compromise the physician's duty and loyalty toward the patient and may seriously harm the patient's trust in the physician.

An underlying principle of managed care is continuity of services which should have a positive impact on the patient-physician relationship. However, the continuity of medical care with a single primary care physician under managed care is also in doubt because patients may change employers and hence have to change to another plan, or an employer may decide to change plans thereby forcing other members of the family to switch as well, and people reaching retirement age have to shift from managed care to Medicare (17). Also, market forces may cause small HMOs to close leaving patients to find new physicians.

In addition to the physician's role in making rationing decisions in a managed care system, the patient must also be involved. Patient preferences, desires, and values need to be considered but require full and accurate disclosure of what is covered and what is not covered by the plan. Competing HMOs promote themselves to consumers as offering lower cost, greater range of benefits, and higher quality of care than their competition. Such advertising disguises the limitations of the plans and patient's expectations may be unrealistic or uninformed leading to patient-provider conflicts when the truth finally becomes known.

Patient satisfaction with their physician and/or their managed care plan may decrease. The physician must maintain the patient's confidence and confidentiality. The physician is also morally obligated to disclose to the patient any conflicts of interest, available or unavaliable alternatives, and rules about restrictions or referrals for consultation and expensive testing. The ethical physician in a managed care environment must convince his/her employer, managed care company, or insurance carrier to authorize the ethically directed appropriate and indicated care. The physician must fight on behalf of the patient. The physician's role as patient advocate must not be compromised.

Universal access to health care is a moral ideal, if not an imperative, based in part on traditional Judeo-Christian ethics. Health care reform is upon us and is inevitable largely because of the high cost of medical care in this country. Physicians are partly responsible for the need for cost containment in that they have for decades practiced medicine without concern for cost and sometimes even abused the system for financial gain. The gold standard of medical practice has always been and should continue to be the patient and not the doctor's best interests. Physicians must be advocates for their patients before they consider their own autonomy, income, and prerogatives.

Some people consider the term managed care to be euphemism for cost containment or rationing. Managed care is also a euphemism for converting medical decision making into business decision making. Relman (2) believes that managed care is unnecessary as a rationing tool because there is considerable fat and waste in the present system.

Quality of care is being redefined not as excellence of care but minimally acceptable care. The controlled use of resources to reduce the cost of medical care may be desirable and helpful, but overmanagement can also lead to a decrease in the quality of care.

Outcome Data

Outcome data about quality of care are still sparse, although trends are beginning to emerge. Miller and Luft (23) found that HMOs, when compared with indemnity plans, had lower hospital admission rates, shorter lengths of stay, the same or more physician office visits per enrollee, less use of expensive procedures and tests, greater use of preventive services, mixed results on outcomes, and somewhat lower enrollee satisfaction with services but higher satisfaction with costs. Udvarhelyi et al. (24) reported that the quality and quantity of ambulatory care for HMO patients was equal to or better than that for fee-for-service patients.

Greenfield et al (25) found no meaningful differences in the mean health outcomes for patients with hypertension or non-insulin-dependent diabetes, whether they were treated by different health care systems or by different physician specialists. This study was criticized by Fihn (26) as being an observational study, limited to two conditions, small numbers of patients, and relatively short follow-up. Other investigators have also shown that patients with rheumatoid arthritis fare equally well under the care of a competent generalist or specialist in a managed care or fee-for-service setting (27). Among patients with acute low back pain, the outcomes were similar whether they received care from primary care practitioners, chiropractors, or orthopedic surgeons; the least expensive care was provided by the primary care practitioners (28).

On the other hand, Safran et al. (29) found notable differences in core dimensions of primary care quality in each of three payment systems and raised questions regarding the associated cost efficiencies and outcomes of care. However, this study was limited to surveys of patient perception and patient satisfaction and did not directly evaluate information on the patients' clinical management or their clinical outcomes (30). Outcomes research is obviously important to make health care more effective (31) by informing decision makers—including public and private payers, but especially physicians and patients—and to help them make better decisions (32).

Comment

The ethics of medical care should be totally divorced from the costs of rendering that care, but pragmatic and political reasons make this unlikely. Clearly, managed care and managed competition are cost driven and not care driven. Physicians under managed care must remain advocates for their patients. "The physician is inescapably a moral accomplice if harm is done to the patient" (15) and must appeal unjust rules and regulations about the restriction of technology and consultation if the patient clearly needs them. The physician must always recommend and do what is best for the patient and not become a functionary of the system. Although the patient-physician relationship under managed care may be somewhat distorted, the patient's interests can and must be safegarded. Patients should not view their provider as a case manager or a gatekeeper but as a caring and concerned physician who works under certain restrictions dictated by social values and cost considerations. Patients must be told what is not covered in their plan for them to exercise their decision making autonomously.

The term "managed care" is said to be an oxymoron because "care" requires flexibility and judgment, whereas "managed" implies rigidity and rules. Managed care thus intrudes on and limits the physician's autonomy. Managed care offers certain options but the one desired by the physician or patient may not be one of those offered. Physicians and patients may not even understand the exclusions, limitations, and gatekeeping of some HMOs. The art of medicine must still take precedence over the business of medicine.

Many unanswered questions—ethical, social and financial—remain under a managed care system. Quality-of-life issues need to be addressed and may vary from patient to patient. Should society pay for liver transplants for alcoholic patients who continue to abuse alcohol? Should society pay for expensive chemotherapy for lung cancer patients who smoked cigarettes all their lives? Should society pay to repair a tennis elbow in a patient who failed to heed medical advice that might have obviated the need for surgery? Should society pay for replacement of an osteoarthritic knee in an elderly patient? Who will pay for new technology under managed care? Who will pay and conduct research for new drug development? How will public health needs be funded?

Managed care does not address related issues which have substantially contributed to the high cost of medical care such as undergraduate, graduate, and continuing medical education, malpractice litigation, and the oversupply and maldistribution of specialist physicians. These topics are important and must be dealt with in a managed care environment.

Position Statement of the Medical Society of the State of New York

The Committee on Bioethical Issues of the Medical Society of the State of New York fully supports the June 1994 report on ethical issues in managed care written by the Council on Ethical and Judicial Affairs of the American Medical Association (22). The report states:

1. The duty of patient advocacy is a fundamental element of the physician-patient relationship that should not be altered by the system of health care delivery in which physicians practice. Physicians must continue to place the interests of their patients first.
2. When managed care plans place restrictions on the care that physicians in the plan may provide to their patients, the following principles should be followed:
   a. Any broad allocation guidelines that restrict care and choices, which go beyond the cost/benefit judgments made by physicians as a part of their normal professional responsibilities, should be established at a policy-making level so that individual physicians are not asked to engage in *ad hoc* bedside rationing.
   b. Regardless of any allocation guidelines or gatekeeper directives, physicians must advocate for any care they believe will materially benefit their patients.
   c. Physicians should be given an active role in contributing their expertise to any allocation process and should advocate for guidelines that are sensitive to differences among patients. Managed care plans should create structures similar to hospital medical staffs that allow physicians to have meaningful input into the plan's development of allocation guidelines. Guidelines for allocating health care should be reviewed on a regular basis and updated to reflect advances in medical knowledge and changes in relative costs.
   d. Adequate appellate mechanisms for both patients and physicians should be in place to address disputes regarding medically necessary care. In some circumstances, physicians have an obligation to initiate appeals on behalf of their patients. Cases may

arise in which a health plan has an allocation guideline that is generally fair but in particular circumstances results in unfair denials of care, i.e., denial of care that, in the physician's judgement, would materially benefit the patient. In such cases, the physician's duty as patient advocate requires that the physician challenge the denial and argue for the provision of treatment in the specific case. Cases may also arise when a health plan has an allocation guideline that is generally unfair in its operation. In such cases, the physician's duty as patient advocate requires not only a challenge to any denials of treatment from the guidelines but also advocacy at the health plan's policy-making level to seek an elimination or modification of the guidelines.

Physicians should assist patients who wish to seek additional, appropriate care outside the plan when the physician believes the care is in the patient's best interests.

   e. Managed care plans must adhere to the requirement of informed consent that patients be given full disclosure of material information. Full disclosure requires that managed care plans inform potential subscribers of limitations or restrictions on the benefits package when they are considering entering the plan.
   f. Physicians also should continue to promote full disclosure to patients enrolled in managed care organizations. The physician's obligation to disclose treatment alternatives to patients is not altered by any limitations in the coverage provided by the patient's managed care plan. Full disclosure includes informing patients of all their treatment options, even those that may not be covered under the terms of the managed care plan. Patients may then determine whether an appeal is appropriate, or whether they wish to seek care outside the plan for treatment alternatives that are not covered.
   g. Physicians should not participate in any plan that encourages or requires care at below minimum professional standards.

3. When physicians are employed or reimbursed by managed care plans that offer financial incentives to limit care, serious potential conflicts are created between the physicians' personal financial interests and the needs of their patients. Efforts to contain health care costs should not place patient welfare at risk. Thus, financial incentives are permissible only if they promote the cost-effective delivery of health care and not the withholding of medically necessary care.
   a. Any incentives to limit care must be disclosed fully to patients by plan administrators on enrollment and at least annually thereafter.
   b. Limits should be placed on the magnitude of fee withholds, bonuses, and other financial incentives to limit care. Calculating incentive payments according to the performance of a sizable group of physicians rather than on an individual basis should be encouraged.
   c. Health plans or other groups should develop financial incentives based on quality care. Such incentives should complement financial incentives based on the quantity of services used.
4. Patients have an individual responsibility to be aware of the benefits and limitations of their health care coverage. Patients should exercise their autonomy by public participation in the formation of benefits packages and by prudent selection of health care coverage that best suits their needs.

Epilogue

Before 1985 and the prospective payment system, hospitals were paid on a cost-plus basis and most physicians were paid on a fee-for-service basis. DRGs introduced cost containment and encouraged early discharge, fewer tests, and restriction of expensive drugs and high-cost technology. The demand for health care is endless and the longer we live, the more it costs. For better or worse, managed care is here to stay. We must understand it and develop methods to work with it, preserving the overriding principle that the physician's first obligation is to be the patient's advocate. Ethics must not take a back seat to cost containment.

Physicians must continue to practice good medicine, eliminate that which is unnecessary, and be conscious of the need to contain costs. Such medial practice should be effective, beneficial, and minimize burdens (financial, social, and personal). Physicians must strive for patient satisfaction and practice within the areas that they are credentialed and do so in the best interests of their patients, not themselves or the HMOs.

References

1. Managed care: a health strategy for today and tomorrow. Washington, DC: Health Insurance Association of America, 1993.

2. Relman AS. Controlling costs by "managed competition"—would it work? N Engl J Med 1993; 328:133–135.
3. Iglehart JK. The American healthcare system. Managed care. N Engl J Med 1992; 327:742–747.
4. Enthoven A, Kronick R. A consumer-choice health plan for the 1990s. Universal health insurance in a system designed to promote quality and economy. N Engl J Med 1989; 320:29–37, 94–101.
5. Enthoven AC, Kronick R. Universal health insurance through incentives reform. JAMA 1991; 265:2532–2536.
6. Rice T, Brown ER, Wyn R. Holes in the Jackson Hole approach to health care reform. JAMA 1993; 270:1357–1362.
7. Pellegrino ED. Ethics. JAMA 1994; 271:1668–1670.
8. Reinhardt UE. Managed competition in health care reform: Just another American dream, or the perfect solution? J Law Med Ethics 1994; 22:106–120.
9. Ginzberg E. Health care reform. Where are we and where should we be going? N Engl J Med 1992; 327:1310–1312.
10. Angell M. How much will health care reform cost? N Engl J Med 1993; 328:1778–1779.
11. Brody H. Framing the health reform debate. Hastings Center Rep 1994; 24(May-June):7–8.
12. Fleischman AR. Physicians and ethics in the health care reform debate. Hastings Center Rep 1994; 24(May-June):10–11.
13. Brock DW, Daniels N. Ethical foundations of the Clinton administration's proposed health care system. JAMA 1994; 271:1189–1196.
14. Daniels N. Principles for national health care reform. Hastings Center Rep 1994; 24(May-June):8–9.
15. Pellegrino, ED. Managed care and managed competition: some ethical reflections. Calyx 1994; 4:1–5.
16. Angell, M. The doctor as double agent. Kennedy Inst Ethics J 1993; 3:279–286.
17. Emanuel EJ, Brett AS. Managed competition and the patient-physician relationship. N Engl J Med 1993; 329: 879–882.
18. Lundberg GD. United States Health Care System reform: an era of shared sacrifice and responsibility begins. JAMA 1994; 271:1530–1533.
19. Eisenberg JM. The internist as gatekeeper. Preparing the general internist for a new role. Ann Intern Med 1985; 102:537–543.
20. Pellegrino ED. Rationing health care: the ethics of medical gatekeeping. J Contemp Health Law Policy 1986; 2:23–45.
21. Hillman AL, Pauly MV, Kerstein JJ. How do financial incentives affect physicians' clinical decisions and the financial performance of health maintenance organizations? N Engl J Med 1989; 321:86–92.
22. American Medical Association Council on Ethical and Judicial Affairs. Code of medical ethics reports, vol. 5, no. 2, July 1994. Chicago: AMA, Report 60, Ethical issues in managed care, pp. 276–289.
23. Miller RH, Luft HS. Managed care plan performance since 1980. A literature analysis. JAMA 1994;271:1512–1519.
24. Udvarhelyi IS, Jennison K, Phillips RS, Epstein AM. Comparison of the quality of ambulatory care for fee-for-service and prepared patients. Ann Intern Med 1991; 115:394–400.
25. Greenfield S, Rogers W, Mangotich M, Carney MF, Tarlov AR. Outcomes of patients with hypertension and non-insulin dependent diabetes mellitus treated by different systems and specialties. Results from the Medical Outcomes Study. JAMA 1995; 274:1436–1444.
26. Fihn SD. Physicians specialty, systems of health care, and patient outcomes. JAMA 1995; 274:1473–1474.
27. Yelin EH, Shearn MA, Epstein WV. Health outcomes for a chronic disease in prepaid group practice and fee for service settings; the case of rheumatoid arthritis. Med Care 1986; 24:236–247.
28. Carey TS, Garrett J, Jackman A, McLaughlin C, Fryer J, Smucker DR, the North Carolina Back pain Project. The outcomes and costs of care for acute low back pain among patients seen by primary care practitioners, chiropractors, and orthopedic surgeons. N Engl J Med 1995; 333:913–917.
29. Safran DG, Tarlov AR, Rogers WH. Primary care performance in fee-for-service and prepaid health care systems. Results from the Medical Outcomes Study. JAMA 1994; 271:1579–1586.
30. Kelly JT. Evaluating quality performance in alternate health care delivery systems. A critical challenge. JAMA 1994; 271:1620–1621.
31. Tanenbaum SJ. Sounding board: what physicians know. N Engl J Med 1993; 329:1268–1270.
32. Sage WM. Outcomes research. N Engl J Med 1994; 330: 434–435.

Appendix

AMA Code of Medical Ethics Reports: No. 60 Ethical Issues in Managed Care*

Introduction

A PRIMARY CONCERN of medical ethicists for some time has been the absence of any meaningful analysis of the impact of health care delivery market place changes and current legislative reforms on the essential tenets of the patient-physician relationship. Although President Clinton's original reform proposal addressed in broad terms the ethical imperatives supporting universal access, it left virtually unexamined the more fundamental question of the role of the physician in a reformed system where the incentives are dramatically changed and budgets determine the amount of health care spending and services.

In June 1990, the Council issued a report, "Financial Incentives to Limit Care: Financial Implications for HMOs and IPAs," (1) which described the financial incentives that managed care plans offer physicians to limit their provision of care (Policy 140.978, *AMA Policy Compendium*). The report concluded that patient welfare must of course remain the first concern of physicians working in HMOs and IPAs and that physicians must disclose all relevant financial inducements and contractual restrictions that affect the delivery of health care to patients.

With its emphasis on managed care and managed competition, health care reform will greatly increase the ethical concerns raised by managed care. It is therefore essential that the profession and society act now to ensure that managed care techniques are implemented in a way that protects patients and the integrity of the patient-physician relationship.

In this report, the Council reiterates the physcian's commitment to patient welfare first and updates its previous recommendations for physicians. This report discusses in greater detail the potential conflicts of interest faced by physicians practicing in the managed care environment. It then recommends measures to preserve the fundamental duty of physicians as patient advocates by reducing the risk of rationing and inappropriate financial incentives.

**Source:* Council on Ethical and Judicial Affairs, Code of Medical Ethics Reports, American Medical Association, ©1994. Reprinted with permission.

Background

As health care costs have risen, and calls for more cost conscious health care have been made (2), health care insurers increasingly have adopted principles of managed care (3). Several different types of managed care arrangements have gained prominence in the United States health care system, including group and staff model health maintenance organizations (HMOs), independent practice associations (IPAs), and preferred-provider organizations (PPOs). Fee-for-service plans are also using many of the cost-saving techniques of managed care.

Managed care plans use a number of techniques. Some of them are directed at physician behavior. Others are directed at subscribers to the plan (4, 5). For example, managed care plans typically encourage subscribers to seek health care when it is still possible to prevent the development of illness by covering a broad range of preventive and primary care services. In addition, they restrict subscribers to panels of physicians who have agreed to accept lower reimbursements or who may have exhibited a history of practicing lower cost care. (Recently, even experienced, highly competent physicians have been separated from their patients in large "deselection" actions by many major plans.) Managed care plans can also control their subscribers' behavior by denying access to the services of medical specialists until the subscriber has obtained the approval of a primary care physician.

Managed care plans constrain the costs of participating physician practices in several ways as well. The plans often restrict the ability of physicians to perform certain procedures or to order certain medications or diagnostic tests. For example, a physician may need the approval of a radiologist before ordering a test, or a managed care plan might exclude some expensive drugs from the plan's formulary. Managed care plans aggressively use programs of utilization review to detect what they consider unnecessarily costly practice patterns. Sometimes their programs become harassing, intimidating and deceptive.

Managed care plans can also reduce costs by creating economies of scale, by coordinating care among physicians and hospitals, by mandating the use of guidelines or parameters of care and by establishing advanced information systems which provide an improved basis on which to measure quality and efficiency.

Managed care plans also encourage physicians to make cost-conscious treatment decisions through the use of financial incentives. The plans often compensate physicians with capitation fees or a salary. In addition, plans typically employ incentives for physicians to limit their use of diagnostic tests, referrals to other physicians, hospital care or other ancillary services. For example, managed care plans often pay bonuses to physicians, with the amount of the bonus increasing as the plans' expenditures for patient care decrease. Or plans often withhold a fixed percentage of their physicians' compensation until the end of the year to cover any shortfalls in the funds budgeted for expenditures on patient care. If there is no shortfall, or the shortfall can be covered by part of the withheld fees, the remaining withheld fees are returned to the physicians (1).

While efforts to contain costs are critical and while many of the approaches of managed care have an impact, managed care can compromise the quality and integrity of the patient-physician relationship and reduce the quality of care received by patients. In particular, by creating conflicting loyalties for the physician, some of the techniques of managed care can undermine the physician's fundamental obligation to serve as patient advocate. Moreover, in their zeal to control utilization, managed care plans may withhold appropriate diagnostic procedures or treatment modalities for patients.

The Patient-Physician Relationship

Before discussing the potential impact of managed care on the patient-physician relationship, it is important to consider what is at stake. The foundation of the patient-physician relationship is the trust that physicians are dedicated first and foremost to serving the needs of their patients. In the Oath of Hippocrates, trust is a central element in almost all of the ethical obligations of physicians: physicians must keep patients' private information confidential, avoid mischief and sexual misconduct, and give no harmful or death-causing agent. Patients can expect that physicians will come to their aid even if it means putting the physician's own health at risk (6), and they can trust that physicians will do everything in their power to help their patients. It is this trust which enables patients to communicate private information and to place their health, and indeed their lives, in the hands of their physicians (1). Without trust, the success of the healing process would be seriously diminished.

No other party in the health care system is charged with the responsibility of advocating for patients, and no other party can reasonably be expected to assume the responsibility conscientiously. Physicians care for patients directly, are in the best position to know patients' interests, and can advocate within the health care system for patients' needs. Without the commitment that physicians place patients interests first and be agents for their patients alone, there is no assurance that the patient's health and well-being will be protected.

Ethical Concerns

Managed care creates at least two conflicting loyalties for the physician. First, physicians are expected to balance the interests of their patients with the interests of other patients. When deciding whether to order a test or procedure for a patient, the physician must consider whether the slot should be saved for another patient or not used at all to conserve the plan's resources. Second, managed care can place the needs of patients in conflict with the financial interests of their physicians. Managed care plans use bonuses and fee withholds to make physicians cost conscious. As a result, when physicians are deciding whether to order a test, they will recognize that it may have an adverse impact on their income.

Some commentators argue that market forces will ensure that patients are protected from undue conflicts of interest. Because subscribers are theoretically free to choose their managed care organization based on quality of coverage, performance record, and other factors, they can theoretically drive those managed care organizations with the least impressive records out of business. However, it is unlikely that these consumer choices alone will ensure high quality managed care organizations. As stated in a recent editorial, "patient satisfaction depends more on visible amenities and personal relations than on the quality and appropriateness of medical services . . . " (7). The following two sections address the potential conflicts of interest for physicians under managed care.

1. Conflicts Among Patients. While some cost containment can be achieved by eliminating waste and inefficiency, it is also being achieved by limiting the availability of tests or procedures that offer only small or uncertain benefit, or that provide a likely benefit but at great expense. Because managed care plans generally work within a limited budget, and, increasingly, are for profit companies that compete to report favorable results to shareholders (8), the cost of a service will influence whether the service is offered to patients who might benefit from it. Allocation rules are developed by the plans to deal with this issue.

Managed care plans can make these allocation decisions in a number of ways: by developing guidelines that determine for a physician when the service should be offered, by instructing physicians to provide medically necessary care and delegating to the physicians the allocation decisions, or by some combination of allocation guidelines, physician discretion, and oversight.

An example of an allocation decision might involve the use of high osmolar contrast media (HOCM) and low osmolar contrast media (LOCM) in diagnostic imaging procedures (9). Both HOCMs and LOCMs produce images of similar quality, and both are approved by the FDA as safe and effective. Adverse reactions, including "changes in cardiac performance, alterations in renal functions, depression of the central nervous system, pain at the site of injection, flushing, nausea, and vomiting," (12) are somewhat more likely with the use of HOCMs. In addition, fatal adverse reactions with either media are extremely rare and no more likely with HOCMs than LOCMs. However, there is a significant difference in the cost of the two media: LOCMs are considerably more expensive than HOCMs. Where a peripheral arteriography procedure would use about $10 of HOCM, the same procedure would use about $180 of LOCM, an increase of 18 times the HOCM cost (12).

It is not obvious which contrast medium should be used. In fact, the decision to use HOCM or LOCM is essentially a value judgment about the relative costs and benefits of the two different media. While medical expertise is necessary to determine what benefits and risks are associated with the two media, the weighing of those benefits and risks with financial costs is not simply a medical decision but also a social judgment about the value of spending additional resources to lower health risks in this manner.

A more difficult allocation case involves the use of bone marrow transplants for certain kinds of advanced cancer. The stakes for the patient are high—a prolonged life if successful—but the costs are great and the likelihood of success uncertain. Some plans will restrict or discourage the treatment; others may make it available under some circumstances.

a. Ethical problems with "bedside rationing." Physicians make cost benefit judgments every day as a part of their professional responsibility in treating patients. It is unethical to knowingly provide unnecessary care or to be wasteful in providing needed care. Except to the extent that the liability system causes them to behave defensively in certain situations, physicians in general make fair and appropriate cost benefit judgments. It has been demonstrated that, even in an exclusively fee for service system, physicians overall respond properly to credible information about the effectiveness of their practices. A primary problem has been good data.

Allocation judgments about costs and services that approach a "rationing" decision—the denial of a procedure that benefits a patient—are not part of the physician's traditional role and, indeed, conflict with it. Although physicians have traditionally served as de facto gatekeepers to the health care system, overseeing the public's use of medical care, the cost primacy environment of managed care significantly complicates this role (10). As Pellegrino has written, "This [gatekeeper] role is morally dubious because it generates a conflict between the responsibilities of the physician as a primary advocate of the patient and as guardian of society's resources" (14). While this responsibility to guard society's resources is an important one, physicians must remain primarily dedicated to the health care needs of their individual patients.

The primary care physician's role in managed care illustrates the ethical problems associated with bedside rationing. The physician-gatekeeper determines whether the patient will be granted further access to the health care system, including referrals to specialists and diagnostic tests. At the same time, the physician is required by rules and encouraged by incentives to be aware of the overall financial limitations of the managed care entity for which he or she works (4). The physician knows that there are other patients who have subscribed to the managed care plan to whom is owed a certain level of health care (11). These competing concerns mean that a patient's further treatment depends not only on the physician's judgment about the legitimacy of that patient's present medical need but also on the relative weight of that need in comparison with the organization's need to serve all patients and control costs. Inconsistent and uninformed decisions are inevitable.

The primary care physician has the greatest responsibility within the managed care organization to assess the seriousness of patients' conditions accurately. A keen understanding of common and uncommon health problems is therefore required, as it is of all primary care physicians. However, the pressures of cost containment may encourage some physicians to try to manage cases longer than they should. Physicians may feel compelled to stretch their competence in order to keep patients at the primary care level and conserve resources. Inappropriate treatment and improper or missed diagnoses are potential outcomes of such decisions to delay or deny referral.

b. Preserving the physician's role. The physician is obligated to provide or recommend treatment when the physician believes that the treatment will materially benefit the patient and not to withhold the treatment to preserve the plan's resources. Physicians should not engage in bedside rationing.

But many allocation rules are within arguable ranges or grey areas of at least minimally acceptable treatment. There are two steps to reducing physician/patient conflict in these circumstances. First, physicians should contribute their expertise in the development of the guidelines and should advocate for the consideration of differences among patients. For example, it might be advisable for a certain group of patients at high risk to be offered LOCM while others who do not fall in this group to be offered HOCM. Physicians can help to ensure that all medically relevant information is considered and that no group of patients is put at an unfair disadvantage.

Second, and most importantly, even if the use of the LOCM were prohibited by a guideline for all or a particular class of patients, it remains the physician's duty to recommend its use and to advocate for the patient's right to the treatment in any case where material benefit to a particular patient would result.

The structure through which physicians offer their expertise in policy-level decisions is very important. To help define this structure, the American Medical Association recently proposed legislation that would require managed care organizations to establish a medical staff structure, much like that in existence in every hospital in the United States. This proposal includes a governing board for the managed care organization that would include at least three physician members as representatives of participating physicians, and a medical board composed entirely of participating physicians. Physicians on the medical board would be responsible for periodically reviewing restrictions on services to subscribers and other issues related to health care coverage. They would also review quality of care and physician credentialing on a periodic basis and disclose their review criteria to subscribers. The governing board would be ultimately responsible for the activities of the managed care organization, but participating physicians would have formal mechanisms for input and responsibilities on crucial medical practice issues.

In addition to the physician's role in making rationing decisions, there is an equally critical role for patients. The decision-making process should include some mechanism for taking into account the preferences and values of the people whom the rationing decisions will most directly affect. Accurate and full disclosure is most important. In addition, a managed care organization could use "town meetings" and other mechanisms whereby subscribers could voice their preferences or "vote" on what treatments should be included in their benefits package (11).

Once guidelines and criteria are developed at the policy level, physicians are free to make clinical decisions based on those guidelines and criteria. For example, if a managed care plan decided to offer LOCM only to patients at high risk for an adverse reaction to HOCM, physicians would decide which patients are at the high risk.

In addition to the development of appropriate procedures for making allocation decisions, there are other steps that must be taken to protect patient welfare when the allocation procedures are implemented. For example, as part of the process of giving patients informed consent to treatment, physicians should disclose all available treatment alternatives, regardless of cost, including those potentially beneficial treatments that are not offered under the terms of the plan. As described in the Council's report on financial incentives to limit care, obligations of disclosure always apply to the physician practicing in managed care. With full understanding of the limitations affecting their treatment, patients will have the opportunity to make alternative arrangements for care that is not available in their health plan.

It is also critical for managed care plans to have a well-structured appeals process through which physicians and patients can challenge the denial of a particular diagnostic test or therapeutic procedure. Such a process should afford the physician an opportunity to advocate on the patient's behalf before the plan's medical board or governing board. Appeals mechanisms for treatment denials are essential because policy-level allocation decisions can never fully account for all contingencies and will sometimes underserve individual patients. Managed care plans, as institutions, have an ethical responsibility to allow patients to challenge treatment decisions that directly affect their health and well-being.

In some circumstances, as noted above, physicians have an obligation to initiate appeals on behalf of their patients. Cases may arise in which a health plan has an allocation guideline that is generally fair but in particular circumstances results in unfair denials of care, i.e., denial of care that would materially benefit the patient. In such cases, the physician's duty as patient advocate requires that the physician challenge the denial and argue for the provision of treatment in the specific case. Cases may also arise when a health plan has an allocation guideline that is generally unfair in its operation. In such cases, the physician's duty as patient advocate requires not only a challenge to any denials of treatment from the guideline but also advocacy at the health plan's policy-making level to seek elimination or modification of the guideline.

2. Conflicts Between Physician and Patient. *a. Ethical problems with financial incentives to limit care.* As discussed above, managed care plans encourage physicians to be more cost conscious by using bonuses, fee withholds and other financial incentives to limit care. With these incentives, physicians recognize that they may reduce their income when they order tests, hospitalize patients or provide other services. The incentives are not inherently unethical, but they can be depending on their design and intensity.

There are two important ways in which financial incentives to limit care compromise the physician's duty of loyalty to patient care. First, physicians have an incentive to cut corners in their patient care, by temporizing too long, eschewing extra diagnostic tests, or refraining from an expensive referral. Several studies have tried to measure the health outcomes of patients in managed care or pre-paid settings against the health outcomes of patients in fee-for-service arrangements. Although disturbing anecdotes abound, these studies have found largely mixed results: (12) harm or inadequate health outcomes have not been conclusively demonstrated in managed care arrangements (13, 14), though these patients may be at an increased risk of harm (15–17). Second, even in the absence of actual patient harm, the incentives may erode patient trust as patients wonder whether they are receiving all necessary care or are being denied care because of the physicians' pecuniary concerns.

Physicians must place patients' interests ahead of their own interests, including financial remuneration (15). It is true that financial conflicts are inherent in the practice of medicine, regardless of the system of delivery, and that physicians generally have been able to maintain their duty to patient welfare despite those conflicts. However, incentives to limit care are more problematic than incentives to provide care.

First, financial incentives to limit care exploit the financial motive of physicians, making the physician's financial self-interest indispensable for the success of the managed care organization. Second, financial incentives to limit care are less likely than financial incentives created by fee-for-service to coincide with patients' interests, because patients generally prefer the risk of too much care to the risk of too little care. Third, the effects of incentives to limit care are less likely to be noticed by patients. When a physician recommends a course of action under fee-for-service reimbursement, the patient can seek a second opinion. However, when a physician does not offer an intervention under managed care, the patient may have no idea that a treatment option was withheld and therefore not recognize the need for a second opinion (11).

Not all financial incentives to limit care create the same conflict of interest between the physician's and patient's interests. In general, the greater the strength of the incentive, the more likely it will create a serious conflict of interest which could lead to patient harm. The strength of a financial incentive to limit care can be judged by various factors, including the percentage of the physician's income placed at risk, the frequency with which incentive payments are calculated, and the size of the group of physicians upon which the economic performance is judged.

If the managed care plan places 30% of a physician's income at risk, the physician will be much more conscious of costs than if the plan places 5% of income at risk. Similarly, if a physician's incentive payments are based solely on his or her treatment decisions, there is a strong incentive to limit services for each patient. When payments are based on the performance of a group of physicians, on the other hand, the incentive is diminished. When physicians are placed at risk together, they have an incentive to ensure that their colleagues are practicing in a cost-effective manner and the incentive payments will be based on costs incurred by a large patient pool. When the patient panel is small, there is a risk that treatment costs will be skewed by an unrepresentative group of patients who have unusually high needs for medical care.

The strength of a financial incentive can also vary with the frequency of incentive payments. If payments are made on a monthly basis rather than a yearly basis, the physician receives rapid feedback on the economic consequences of treatment decisions and is therefore likely to be more sensitive to those consequences. In addition, when incentives are calculated on a monthly basis, there is less of an opportunity for the costs of cases that are above average to be offset by the costs of cases that are below average. Accordingly there is a stronger incentive not to incur unusually high expenses in any one case.

b. *Preserving the physician's role.* The most effective way to eliminate inappropriate conflicts is to create the use of financial incentives based on quality rather than quantity of services. Reimbursement that serves to promote a standard of "appropriate" behavior helps to maintain the goals of professionalism. Unlike incentives based on quantity of services, which punish the provision of both appropriate and inappropriate services, incentives based on quality of care punish only inappropriate services.

Judgments about the quality of a physician's practice should reflect several measures. First, it is essential to consider objective outcomes data, including data about mortality and morbidity, corrected for caseload. Second, because outcomes are often beyond the physician's control, it is important to consider the degree to which the physician adheres to practice guidelines or other standards of care. Third, patient satisfaction should be considered. Although patients are limited in their ability to evaluate physician competence, they are the best judges of one critical quality of physician care, the physician's "bedside manner." In addition, patient satisfaction reflects the extent to which the physician has accommodated the goals of the patient, as required by the patient's right to exercise self-determination in medical care. Fourth, the judgment of a physician's peers generally reflects the best available assessment of quality.

Because measurements of quality are still in the rudimentary stages of development, it is important to ensure that other safeguards are in place to prevent abuse from incentives based on quantity of care. Reasonable limits should be placed on the extent to which a physician's ordering of services can affect his or her income. For example, quantitative financial incentives should be calculated on groups of physicians rather than individual physicians.

Patient Autonomy and Responsibility

Many commentators argue that managed care threatens patient autonomy because it curtails patients' freedom of choice. Patients are usually limited in their choice of primary care physicians and, to a much greater degree, specialists, and they are sometimes limited in their choice of treatments. Patients may not be able to receive a desired diagnostic test or referral, and their freedom to personally tailor treatment can be thwarted. In addition, continuity of care may be disrupted if a patient is forced, for a variety of reasons, to change physicians in order to keep their health care benefits (18).

Public participation in the formulation of benefits packages may resolve some of these concerns about limited autonomy. Legislation reasonably protecting patients' rights to be informed and to choose, and protecting physicians' rights to remain professionals, is also essential. Patients can exercise their autonomy by participating in the decisions of their health plan or in government processes that may restrict their choices or their benefits. In addition, patients have a responsibility to learn as much as they can about the choices of plans before them, including the exact nature of the different benefits packages and their limitations. Patients have a responsibility to make sure they know and understand the terms of their own health care plan.

As patient advocates, physicians continue to have duties of disclosure. They must ensure that all treatment alternatives, regardless of cost, are disclosed. They must also ensure that the managed care organization has fulfilled its obligation to disclose the terms of the benefits package, including all limitations and restrictions.

Patient autonomy does not guarantee the right to have all treatment choices funded. Some limits on personal freedom are inevitable in a society which tries to provide all of its members with adequate health care. The desire for accurate diagnosis and use of high tech medical care, no matter how little the benefit, has been cited as a major factor in health care costs in this country (19). Moreover, patient autonomy entails patient responsibility, including a responsibility to abide by societal decisions to conserve health care and to make an individual effort to use resources wisely and lead a healthy lifestyle.

While physicians must remain patient advocates, patients do not have an unlimited claim to physicians' obligation to provide health care. Physicians should not manipulate or "game" the system in order to answer patients' demands (20).

In order to fully exercise their autonomy, patients need to be fully informed about the philosophy and goals of managed care. In an earlier report, the Council stated that the physician's responsibilities under managed care include a duty to disclose to the patient conflicts of interest that may affect patient care and medical alternatives that cannot be offered because of the restrictions of the managed care plan. That report specifically states that physicians have a duty to disclose financial incentives; a duty to disclose contractual agreements restricting referral; and a duty to ensure that the managed care plan makes adequate disclosure of the details of the plan to subscribers (1, 21).

Recommendations

For the reasons described in this report, the Council on Ethical and Judicial Affairs recommends that the following guidelines be adopted and the remainder of this report be filed:

1. The duty of patient advocacy is a fundamental element of the physician-patient relationship that should not be altered by the system of health care delivery in which physicians practice. Physicians must continue to place the interests of their patients first.

2. When managed care plans place restrictions on the care that physicians in the plan may provide to their patients, the following principles should be followed:

(a) Any broad allocation guidelines that restrict care and choices—which go beyond the cost/benefit judgments made by physicians as a part of their normal professional responsibilities—should be established at a policy making level so that individual physicians are not asked to engage in ad hoc bedside rationing.

(b) Regardless of any allocation guidelines or gatekeepter directives, physicians must advocate for any care they believe will materially benefit their patients.

(c) Physicians should be given an active role in contributing their expertise to any allocation process and should advocate for guidelines that are sensitive to differences among patients. Managed care plans should create structures similar to hospital medical staffs that allow physicians to have meaningful input into the plan's development of allocation guidelines. Guidelines for allocating health care should be reviewed on a regular basis and updated to reflect advances in medical knowledge and changes in relative costs.

(d) Adequate appellate mechanisms for both patients and physicians should be in place to address disputes regarding medically necessary care. In some circumstances, physicians have an obligation to initiate appeals on behalf of their patients. Cases may arise in which a health plan has an allocation guideline that is generally fair but in particular circumstances results in unfair denials of care, i.e., denial of care that, in the physician's judgment, would materially benefit the patient. In such cases, the physician's duty as patient advocate requires that the physician challenge the denial and argue for the provision of treatment in the specific case. Cases may also arise when a health plan has an allocation guideline that is generally unfair in its operation. In such cases, the physician's duty as patient advocate requires not only a challenge to any denials of treatment from the guideline but also advocacy at the health plan's policy-making level to seek an elimination or modification of the guideline.

Physicians should assist patients who wish to seek additional, appropriate care outside the plan when the physician believes the care is in the patient's best interests.

(e) Managed care plans must adhere to the requirement of informed consent that patients be given full disclosure of material information. Full disclosure requires that managed care plans inform potential subscribers of limitations or restrictions on the benefits package when they are considering entering the plan.

(f) Physicians also should continue to promote full disclosure to patients enrolled in managed care organizations. The physician's obligation to disclose treatment alternatives to patients is not altered by any limitations in the coverage provided by the patient's managed care plan. Full disclosure includes informing patients of all of their treatment options, even those that may not be covered under the terms of the managed care plan. Patients may then determine whether an appeal is appropriate, or whether they wish to seek care outside the plan for treatment alternatives that are not covered.

(g) Physicians should not participate in any plan that encourages or requires care at below minimum professional standards.

3. When physicians are employed or reimbursed by managed care plans that offer financial incentives to limit care, serious potential conflicts are created between the physicians' personal financial interests and the needs of their patients. Efforts to contain health care costs should not place patient welfare at risk. Thus, financial incentives are permissible only if they promote the cost-effective delivery of health care and not the withholding of medically necessary care.

(a) Any incentives to limit care must be disclosed fully to patients by plan administrators upon enrollment and at least annually thereafter.

(b) Limits should be placed on the magnitude of fee withholds, bonuses and other financial incentives to limit care. Calculating incentive payments according to the performance of a sizable group of physicians rather than on an individual basis should be encouraged.

(c) Health plans or other groups should develop financial incentives based on quality of care. Such incentives should complement financial incentives based on the quantity of services used.

4. Patients have an individual responsibility to be aware of the benefits and limitations of their health care coverage. Patients should exercise their autonomy by public participation in the formulation of benefits packages and by prudent selection of health care coverage that best suits their needs.

June 1994.

References

1. Council on Ethical and Judicial Affairs. Financial incentives to limit care: Financial implications for HMOs and IPAs, Vol 1. Reports of the Council on Ethical and Judicial Affairs of the AMA. Chicago, IL: American Medical Association; 1990.
2. Enthoven A, Kronick R. A consumer-choice health plan for the 1990s: Universal health insurance in a system designed to promote quality and economy. N Engl J Med. 1989; 320:29–37.
3. Povar G, Moreno J. Hippocrates and the health maintenance organization. Ann Intern Med 1988; 109:419–424.
4. Iglehart JK. The American health care system: managed care. N Engl J Med 1992; 327:742–747.
5. Principles of managed care. A summary of American Medical Association Policy. Chicago, IL: American Medical Association, 1993.
6. Council on Ethical and Judicial Affairs. Ethical issues involved in the growing AIDS crisis. JAMA 1988; 259: 1360–1361.
7. Relman AS. Medical practice under the Clinton reforms. N Engl J Med 1993; 329:1574–1576.
8. Morreim EH. Cost containment: challenging fidelity and justice. Hastings Center Report December 1988: 20–25.
9. Board of Trustees. How cost containment may affect the standard of care in medical malpractice litigation. Proceedings of the House of Delegates of the American Medical Association. Chicago, IL: American Medical Association, June 1991.
10. Pellegrino ED. Rationing health care: The ethics of medical gatekeeping. Journal of Contemporary Health Law and Policy. 1986; 2:23–45.
11. Council on Ethical and Judicial Affairs. Ethical issues in health system reform: The provision of adequate health care. Reports of the Council on Ethical and Judicial Affairs of the AMA. Chicago, IL: American Medical Association; 1994.
12. Miller RH, Luft HS. Managed care plan performance since 1980: a literature analysis. JAMA 1994; 271:1512–1519.
13. Rubenstein LV, et al. Changes in quality of care for five diseases measured by implicit review, 1981–1986. JAMA 1990; 264:1974–1979.
14. Kahn KL, et al. Comparing outcomes of care before and after implementation of the DRG-based prospective payment system. JAMA 1990; 264:1984–1988.
15. Kosecoff, J, et al. Prospective payment system and impairment at discharge: the "quicker-and-sicker" story revisted. JAMA 1990; 264:1980–1983.

16. Ware JE, Jr., et al. Comparison of health outcomes at a health maintenance organisation with those of fee-for-service. The Lancet 1986; May 3:1017–1022.
17. Clement DG, Retchin SM, Brown RS, Stegall MH. Access and outcomes of elderly patients enrolled in managed care. JAMA 1994; 271:1487–1492.
18. Emanuel EJ, Brett AS. Managed competition and the patient-physician relationship. N Engl J Med 1993; 329: 879–882.
19. Kassirer JP. Our stubborn quest for diagnostic certainty: A cause of excessive testing. N Engl J Med 1989; 320: 1489–1491.
20. Morreim EH. Gaming the system: dodging the rules, ruling the dodgers. Arch Intern Med 1991; 151:443–447.
21. Opinion 8.13: Referral of patients—disclosure of limitations. Current Opinions of the Council on Ethical and Judicial Affairs of the AMA. Chicago, IL: American Medical Association, 1992.

The Role of Sex Steroids in the Pathogenesis and Maintenance of Benign Prostatic Hyperplasia

ALICE C. LEVINE, M.D., ALEXANDER KIRSCHENBAUM, M.D., AND J. LESTER GABRILOVE, M.D.

Abstract

Background: It has long been suspected that sex steroids play a key role in the pathogenesis of benign prostatic hyperplasia (BPH). Prostatic diseases do not occur in males castrated before puberty or in males with heritable disorders of androgen production or action. Both estrogens and androgens have been shown to induce BPH in experimental animals.

Methods: Clinical studies utilizing hormonal therapies to treat BPH were reviewed. Studies that used total medical castration therapy via the use of a long-acting gonadotropin-releasing hormone (GnRH agonist), partial androgen blockade via the use of the 5α-reductase inhibitor finasteride, and estrogen blockade (via the use of aromatase inhibitors) were analyzed.

Results and Conclusions: Both the GnRH agonists and finasteride result in prostatic size reduction and alleviate symptoms in some patients. Both therapies are more effective in men with larger prostates (>40 cc). Finasteride is less efficacious in terms of size reduction than the GnRH agonists but also has fewer side effects. To date, clinical trials with aromatase inhibitors have not yielded dramatic positive results in the treatment of BPH.

BENIGN PROSTATIC HYPERPLASIA (BPH) is the most common benign neoplasm in men. Although surgery is still the gold standard of treatment for BPH, the morbidity of surgery has led to the search for and development of noninvasive forms of therapy. The goals of therapy are to reverse the established disease process to some extent, but, more importantly, to interfere with the natural history of the disorder. To achieve these goals, we need a better understanding of the factors that contribute to both the pathogenesis and clinical symptomology of this common ailment.

It has long been suspected that sex steroids play a role in the pathogenesis of this disorder. With the recent development of pharmacologic agents that interfere with sex steroid production and/or action, it is possible to determine the ongoing role of these hormones in the initiation and maintenance of the hyperplastic prostate.

Leydig cells of the human testis produce and secrete testosterone. Testosterone is metabolized in target tissues to both dihydrotestosterone (DHT), via the enzyme 5α-reductase, and to estradiol (E_2), via the enzyme aromatase. Therefore, when determining the *in vivo* actions of testosterone, one must consider all three of these major sex steroids in the evaluation (Fig. 1).

Androgens

Neither BPH nor prostate cancer occur in males castrated before the age of puberty (1, 2) or in males with heritable disorders of androgen production or action (3). Early studies utilizing surgical castration to treat BPH demonstrated a re-

---

From the Department of Medicine, Division of Endocrinology (ACL, JLG), and the Department of Urology (AK), Mount Sinai School of Medicine, New York, NY 10029. Address reprint requests to Dr. Alice C. Levine, Box 1055, Mount Sinai School of Medicine, Department of Medicine, Division of Endocrinology, 1 Gustave L. Levy Place, New York, NY 10029.

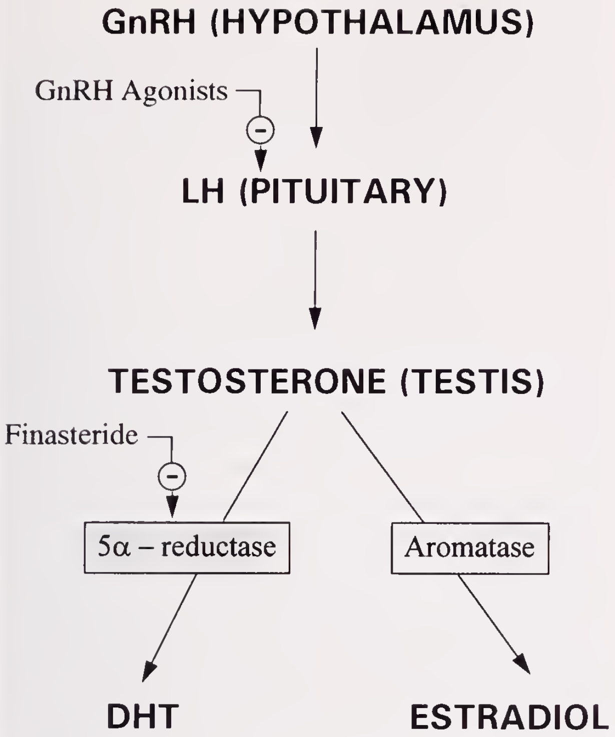


Fig. 1. Metabolic pathways in the production of sex steroids.

gression in prostate size and a decrease in symptoms in the majority of patients (4, 5). Castration, either surgical or medical, lowers serum and tissue levels of testosterone, DHT, and estradiol in males (Fig. 1).

DHT and 5α-Reductase Inhibition

There is some evidence to suggest that DHT is the important androgen which regulates prostatic growth. DHT binds to the same nuclear androgen receptor as testosterone, but does so with a much greater affinity. Patients with heritable deficiencies in the Type 2 isozyme or steroid 5α-reductase (which converts testosterone intracellularly to DHT) develop only rudimentary prostates and have not been reported to develop BPH and prostate cancer (3, 6). In some studies, prostatic tissue levels of DHT have been increased in specimens obtained from patients with BPH (7). We have localized the Type 2 isozyme of steroid 5α-reductase in the human fetal prostate and adult hypertrophied prostate to prostatic stromal cells and periurethral epithelial cells (8). Interestingly, BPH arises in the periurethral area of the prostate, and the initiating event is felt to be the reawakening of the embryonic potential of the BPH stromal cells. Thus, the local expression of 5α-reductase may serve to concentrate this potent androgen, DHT, in critical areas of the human prostate and thereby regulate prostatic growth.

As mentioned, males with 5α-reductase deficiency do not develop benign prostatic hyperplasia or prostate cancer, but reportedly have normal libido and sexual function. For this reason, treatment of BPH with 5α-reductase inhibition held great promise for reducing the symptoms of prostatism without causing sexual dysfunction. In 1992, the 5α-reductase inhibitor, finasteride, became the first medication to be approved for the treatment of BPH. In a large, double-blind, placebo-controlled, multicenter trial, finasteride (5 mg daily) decreased serum DHT levels by 80% and decreased prostate volume, on average, by 19% after 6 months treatment (9). Compared with men in the placebo group, the finasteride-treated men had a significant decrease in total urinary symptom scores and an increase of 1.6 mL/s in the maximal urinary flow rate. In a follow-up study, the average prostate volume reduction in patients receiving finasteride for 36 months was 27% (10).

One of the endpoints of any treatment for BPH is a symptom reduction. The Scandinavian BPH study group reported on a 2-year placebo-controlled study with finasteride (5 mg p.o. daily) in a large group of patients with moderate symptoms of BPH ($n = 707$) (11). In the finasteride-treated group, the symptom scores decreased significantly, although not dramatically, by a mean of 2 points (maximum symptom score = 35 points). Interestingly, in the placebo group, symptom scores initially improved somewhat, but then returned to baseline by the end of the 24-month study. The maximum urinary flow rate decreased in the placebo group but improved in the finasteride-treated patients, resulting in a between-group difference of 1.8 mL/s at 24 months ($p < 0.01$). Prostate volume increased by 12% in the placebo group versus a decrease of 19% in the finasteride-treated group ($p < 0.01$).

Thus, in these studies, finasteride for the treatment of BPH resulted in modest prostate volume reduction and some improvement in symptomatology and maximal urinary flow rates. More importantly, in the placebo groups, there was a trend toward increase in prostatic size and no change in symptomatology or urinary flow rates after 2 years. Finasteride was generally well tolerated without serious side effects. These results imply that finasteride can reverse the natural progression of BPH.

A recent, large, placebo-controlled clinical trial compared the α_1-adrenergic-antagonist drug, terazosin, with the finasteride in terms of symptom reduction in men with BPH (12). In that trial, terazosin alone was effective in reducing symptoms. Finasteride was ineffective alone and did not add any benefit when combined with terazosin. The discrepancy between the combination study results and other clinical trials, which demonstrated that finasteride was effective in reducing symptoms in men with BPH, may be explained by differences in the prostate size of the study populations. In the combined study, prostate enlargement was not a criterion for eligibility and the average prostate volume was only mildly enlarged (approximately 37 cc). A meta-analysis of six randomized clinical trials with finasteride (total number of patients = 2601) revealed that the average prostate size was larger. Initial prostate size is a key predictor of the response to finasteride treatment, with the difference in magnitude of improvement between finasteride and placebo reaching statistical significance for men with baseline prostate volumes >40 cc (13).

However, even in patients with larger prostates, there are some drawbacks to finasteride which may be generalized to all endocrine approaches to this disease. BPH is a heterogeneous disorder, and the response to finasteride is heterogeneous. We have recently demonstrated that, at the present time, there are no good predictors (aside from initial prostate size) of the response to finasteride therapy (14). Although initial prostate size is important (smaller prostates may not respond well), the percentage volume reduction induced by GnRH agonist or finasteride therapy does not correlate with the amount of symptom reduction. Up to one third of patients will have no improvement in symptoms. Finally, hormonal therapies reduce symptomatology by reducing prostate size. The reduction in prostate volume induced by hormonal therapies is slow and gradual. Therefore, the reduction in symptomatology, if it occurs, is also slow and gradual; it may not be perceived by patients as a dramatic change in their disease state.

GnRH Agonist Treatment

Because castration therapy reduces serum and tissue levels of all three of the major sex steroid hormones (testosterone, DHT, and estradiol), the availability of long-acting gonadotropin-releasing hormone agonists (GnRH agonists) made it possible to test the effects of reversible medical castration on prostate size and symptoms in men with BPH.

We reported on the use of a GnRH agonist (leuprolide acetate) in 15 men with symptomatic BPH (15, 16). Castrate serum levels of testosterone, DHT, and estradiol were achieved 4 to 6 weeks after the initiation of therapy in all patients. Mean prostatic volume, as measured by transrectal ultrasonography, decreased by 48% after 6 months treatment. The patients who had the most severe symptoms before treatment (i.e., complete urinary obstruction) had the most dramatic improvement in response to therapy. Four of the five patients who presented with complete urinary obstruction were able to void and have their urinary catheters removed after 3 to 5 months receiving the GnRH agonist treatment. The irritative symptoms of prostatism (frequency, nocturia, urgency) improved somewhat with treatment although less dramatically than the obstructive symptoms. The side effects of treatment were hot flushes and erectile impotence. Surprisingly, in a study by Eri and Tveter (17), the side effects of GnRH agonist therapy, including decreased libido and erectile dysfunction, were well tolerated by the majority of the patients.

Subsequent reports using GnRH agonists to treat BPH demonstrated similar response rates in terms of prostate volume reduction at 6 months (18, 19). In one study, maximum flow rates improved compared with placebo (19). In both studies, a subgroup of patients were treated for longer time periods (up to 1 year). In one study, the maximal decrease in prostatic volume was not reached until 9 months of treatment (18). In the other report, improvement in irritative symptoms in treatment versus placebo groups reached statistical significance only after 48 weeks of treatment (19).

These reports indicate that GnRH agonist therapy is more dramatic than 5α-reductase inhibition in the treatment of BPH, both in terms of benefits and side effects. All of the hormonal therapies have a slow onset of beneficial effects and require at least 6 months of treatment to demonstrate positive results. As with finasteride, the response to treatment is heterogeneous, does not correlate with prostate volume reduction, and cannot be predicted by pretreatment serum prostate-specific antigen values or prostate volume determinations.

The mechanism of prostatic shrinkage with anti-androgen therapy is unclear. Androgens have distinct effects on prostate acinar epithelial cell atrophy and reduction in serum prostate-specific antigen values, a marker of acinar epithelial cells (20). However, the initiating cell type in the BPH process is probably the stroma. Adult prostatic fibroblasts derived from human BPH tissue express androgen receptors and proliferate modestly *in vitro* in response to androgen addition (21). Studies in both the dog and humans indicate that finasteride probably inhibits the growth of stroma as well as epithelium in the prostate (14, 22).

Estrogens

Estrogens have also been suspected of playing a role in the pathogenesis of BPH. Retrospective autopsy studies have revealed two peaks in prostatic growth in humans (23, 24). The first peak in prostatic growth occurs at puberty when androgen levels rise. The second peak in prostatic growth is noted beginning around 50 years of age. The ratio of serum estrogens to androgens increases, on average, in aging men (25, 26). In 1936, Zuckerman postulated that it is the balance between serum estrogens and androgens, rather than absolute values of either hormone, which contribute to the etiology of BPH (27). Several studies have substantiated Zuckerman's hypothesis. In a large study, (n = 640 men) comparing serum hormone values in men with BPH with control, there was a strong trend toward increased BPH risk with increasing serum estradiol levels. Moreover, the excess risk associated with estradiol was confined to men with relatively low androgen levels (28). Another recent study also found that both estradiol levels and estrogen/testosterone ratios were significantly correlated with prostate size (29).

BPH originates as stromal nodules in the periurethral region of the prostate, termed the transition zone (30). In another report, estrogens and age were found to strongly influence transition zone size, but not peripheral zone size or total prostate volumes (31). According to Seppelt (32), there was a highly significant increase in prostate stroma in association with higher plasma estradiol and urinary estrogen excretion, but no correlation with testosterone levels. He also reported that the main prostate change in several species treated with estrogen was an increase in the size of the gland caused by an overgrowth in the fibromuscular component, as well as an atrophic and metaplastic effect on the epithelial component.

Several studies have demonstrated high estrogen levels in BPH stroma (33, 34). It has been postulated that various mechanisms contribute to estrogen accumulation in the prostate. In addition to estrogens obtained from the peripheral circulation, local estrogen may be produced in the stroma via aromatase and sulfatase activities (35).

Immunohistochemical studies have localized estrogen receptor expression to the basal epithelial and stromal cells of human BPH tissue (36, 37). We have also localized estrogen receptor mRNA expression with *in situ* hybridization to prostatic basal epithelial and stromal cells. GnRH agonist therapy, which results in basal cell hyperplasia and squamous metaplasia of basal cells, up-regulated estrogen receptor mRNA expression (38).

Sex hormone-binding globulin, also known as testosterone-estradiol-binding globulin, has played a role in estrogen-mediated effects in the prostate which are distinct from estrogen receptor-mediated effects. Estrogens increase synthesis in the liver 5- to 10-fold (35). Sex hormone-binding globulin, bound to its specific cell-surface receptor in prostatic stroma, can be activated by estrogens to increase intracellular cyclic AMP activity. This estrogen-mediated event does not involve nuclear estrogen receptors (39).

Estrogen administration in dogs and monkeys has increased prostatic stromal proliferation (40–44). In the dog model (which is the only species other than humans that develops spontaneous BPH), estrogen and androgen have synergistic effects on stromal growth (40, 42).

It has been difficult to ascertain the direct effects of estrogen in human studies because of the indirect effects of estrogen via central inhibition of gonadotropins. One study compared prostate volumes and histology in a group of men without BPH who opted for a male-to-female gender assignment. They received either the anti-androgen RU 23908 (Anandron), or the anti-androgen cyproterone acetate in combination with ethinyl estradiol. After 18 months of therapy, there was no difference in prostate volume between the two groups, but the prostates of men who had received estrogen had glandular atrophy and increased stromal tissue (45).

We studied the effects of adding estrogen to GnRH agonist therapy for BPH. The estrogen was added after 6 months treatment with the leuprolide acetate alone. The addition of estrogen therapy did not alter prostate size, serum prostate-specific antigen, or symptoms but resulted in basal cell hyperplasia and squamous metaplasia of basal cells (46). It should be noted, however, that in the study of Eri and Tveter (19), carried out for 12 months, the prostate volume continued to decrease in the 6th to 12th month interval of treatment with a GnRH agonist. This might suggest that the addition of estrogen in our study really prevented the further decrease or indeed increased the prostate volume over its predicted decrease.

Treatment of BPH with estrogen receptor antagonists or aromatase inhibitors holds the promise of targeting prostatic stroma while preserving male potency. Unfortunately, the only estrogen receptor antagonist currently available in the United States is tamoxifen, which is known to have both agonist and antagonist effects *in vivo*. Schweikart and Tunn (47) reported that men with BPH treated with the weak aromatase inhibitor testolactone for a 6-month period had a 26% decrease in prostatic volume with relief of urinary obstruction. A more recent placebo-controlled, double-blind study utilizing the aromatase inhibitor atamestane in the treatment of BPH did not find any difference in clinical symptoms between the atamestane-treated and placebo groups after 48 weeks of therapy (48). In that study, however, it was noted that the aromatase inhibitor decreased serum estrogen levels, while increasing serum androgen levels. The authors postulated that the androgenic effects may have offset any potential benefits from the estrogen inhibition.

Summary and Conclusions

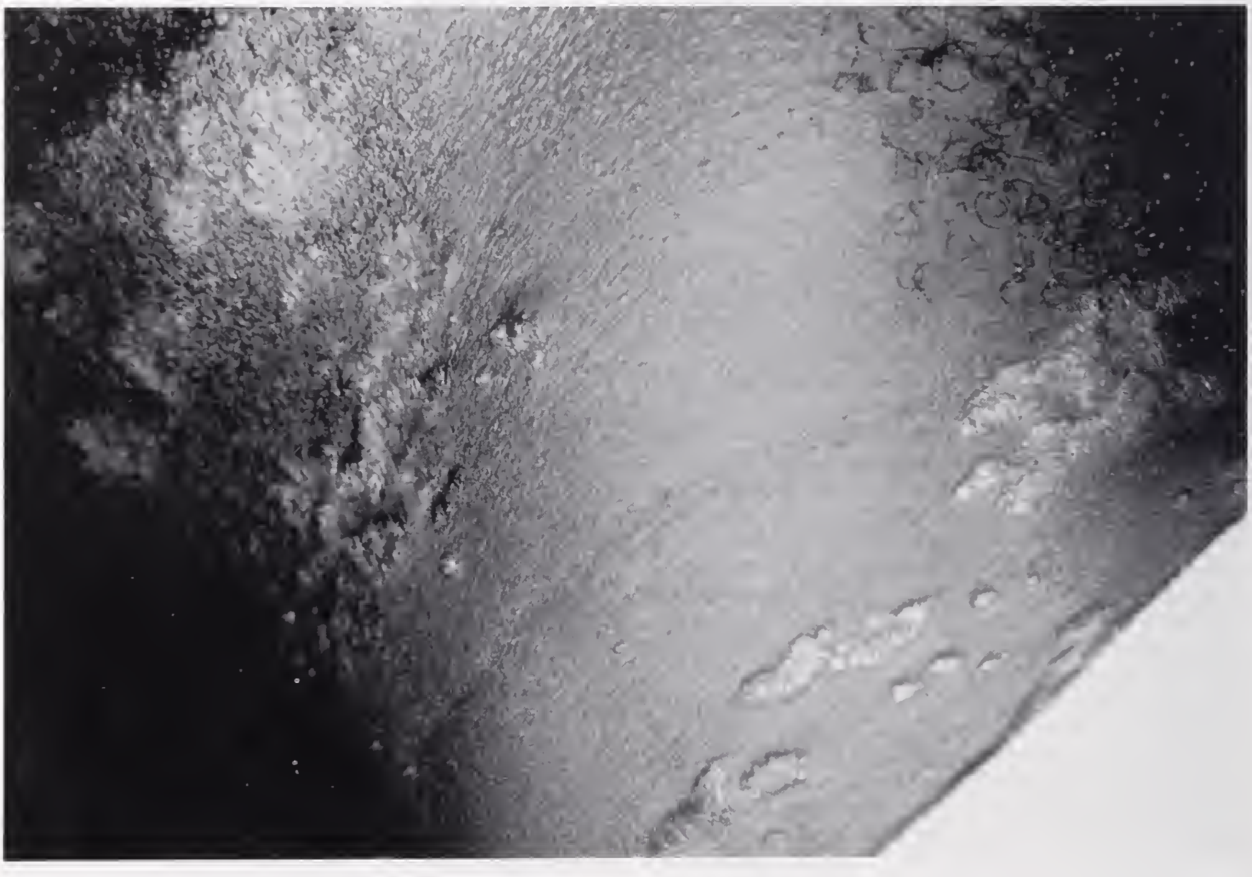
There is considerable evidence that sex steroids play a critical role in the development of BPH. There are also extensive clinical data, in animals and humans, which prove that removal of sex steroids results in regression in prostatic size and the symptoms of prostatism. GnRH agonists, which induce a reversible medical castration and reduce serum levels of androgens and estrogens, have the most potent effects but also the most troubling side effects. Anti-androgens may reduce stromal volume to an extent, but have more clear-cut inhibitory effects on epithelium. Because BPH is primarily a stromal disease, therapies that interfere with estrogen action on stroma might prove to be effective and relatively free of side effects. However, studies to date using aromatase inhibitors to treat BPH have not yielded impressive results. Future studies with more effective estrogen receptor antagonists may determine the influence of estrogens in this common disorder.

References

1. Wilson JD. The pathogenesis of benign prostatic hyperplasia. Am J Med 1990; 68:745–756.
2. Moore RA. Benign hypertrophy and carcinoma of the prostate. Occurrence and experimental production in animals. Surgery 1944; 16:152–167.
3. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5α-reductase deficiency in man: an inherited form of male pseudohermaphroditism. Science 1974; 186:1213–1215.
4. White JW. The results of double castration in hypertrophy of the prostate. Ann Surg 1895; 22:1–80.
5. Cabot AT. The question of castration for enlarged prostate. Ann Surg 1896; 24:265–309.
6. Imperato-McGinley J, Gautier T, Zirinsky K, et al. Prostate visualization studies in males homozygous and heterozygous for 5α-reductase deficiency. N Engl J Med 1992; 327:1185–1191.
7. Siiteri PK, Wilson JD. Dihydrotestosterone in prostatic hypertrophy. I. The formation and content of dihydrotestosterone in the hyperplastic prostate of man. J Clin Invest 1970;49:1737–1745.
8. Levine AC, Wang J-P, Ren M, et al. Immunohistochemical localization of steroid 5α-reductase 2 in the human male fetal reproductive tract and adult prostate. J Clin Endocrinol Metab 1996; 81:384–389.
9. Gormley GJ, Stoner E, Bruskewitz RC, et al. The effect of finasteride in men with benign prostatic hyperplasia. N Engl J Med 1992; 327:1185–1191.
10. Stoner E and the Finasteride Study Group. Three-year safety and efficacy data on the use of finasteride in the treatment of benign prostatic hyperplasia. Urology 1994; 43:284–292.
11. Andersen JT, Ekman P, Wolf H, et al. Can finasteride reverse the progress of benign prostatic hyperplasia? A two-year placebo-controlled study. Urology 1995; 46: 631–637.
12. Lepor H et al. The efficacy of terazosin, finasteride or both in benign prostatic hyperplasia. N Engl J Med 1996; 335:533–539.
13. Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. Urology 1996; 48:398–405.
14. Kirschenbaum A, Pacheco E, Schuval BJ, Levine AC. Lack of correlation between serum prostate specific antigen or prostate specific antigen density and prostate volume reduction in response to finasteride therapy for benign prostatic hyperplasia. World J Urol In press.
15. Gabrilove JL, Levine AC, Kirschenbaum A, Droller M. Effect of a GnRH analogue (leuprolide) on benign prostatic hypertrophy. J Clin Endocrinol Metab 1987; 64: 1331–1333.
16. Gabrilove JL, Levine AC, Kirschenbaum A, Droller M. Effect of long-acting GnRH analogue (leuprolide) on prostatic size and symptoms in 15 men with benign prostatic hypertrophy. J Clin Endocrinol Metab 1989; 69:629–632.
17. Eri LM, Tveter KJ. Safety, side effects and patient acceptance of the luteinizing hormone releasing hormone agonist leuprolide in treatment of benign prostatic hyperplasia. J Urol 1994; 152:448–452.
18. Matzkin H, Chen J, Lewysohn O, Braf Z. Treatment of benign prostatic hypertrophy by a long-acting gonadotropin-releasing hormone analogue: 1-year experience. J Urol 1991; 145:309–312.
19. Eri LM, Tveter KJ. A prospective, placebo-controlled study of the luteinizing hormone-releasing hormone agonist leuprolide as treatment for patients with benign prostatic hyperplasia. J Urol 1993; 150:359–364.
20. Levine AC, Kirschenbaum A, Kaplan P, et al. Serum prostate-specific antigen levels in patients with benign prostatic hypertrophy treated with leuprolide. Urology 1989; 34:10–13.

21. Levine AC, Ren M, Huber GK, Kirschenbaum AK. The effect of androgen, estrogen, and growth factors on the proliferation of cultured fibroblasts derived from human fetal and adult prostates. Endocrinology 1992; 130: 2413–2419.
22. Laroque PA, Prahalada S, Gordon LR, et al. Effects of chronic oral administration of a selective 5α-reductase inhibitor, finasteride, on the dog prostate. Prostate 1994; 24:93–100.
23. Swyer GIM. Postnatal growth changes in the human prostate. J Anat 1944; 78:130–145.
24. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of benign prostatic hyperplasia with age. J Urol 1984; 132:474–479.
25. Pirke KM, Doerr P. Age related changes in interrelationship between plasma testosterone, estradiol and testosterone binding globulin in normal adult males. Acta Endocrinol 1973; 74:729–800.
26. Zumoff B, Strain GW, Kream J, et al. Age variation of the 24-hour mean plasma concentrations of androgens, estrogens and gonadotropins in normal adult men. J Clin Endocrinol Metab 1982; 54:534–538.
27. Zuckerman S. The endocrine control of the prostate. Proc R Soc Med 1936; 29:81–92.
28. Gann PH, Hennekens CH, Longcope C, et al. A prospective study of plasma hormone levels, nonhormonal factors, and development of benign prostatic hyperplasia. Prostate 1995; 26:40–49.
29. Suzuki K et al. Endocrine environment of benign prostatic hyperplasia: prostate size and volume are correlated with serum estrogen concentration. Scand J Urol Nephrol 1995; 29:65–68.
30. McNeal JE. Anatomy of the prostate: an historical survey of divergent views. Prostate 1980; 1:1–13.
31. Meikle AW, Stephenson RA, McWhorter WP, et al. Effects of age, sex steroids, and family relationships on volumes of prostate zones in men with and without prostate cancer. Prostate 1995; 26:253–259.
32. Seppelt U. Correlation among prostate stroma, estrogen levels and urinary estrogen excretion in patients with benign prostatic hypertrophy. J Clin Endocrinol Metab 1978; 47:1230–1235.
33. Kozak I, Bartsch W, Krieg M, Voight KD. Nuclei of stroma: site of highest estrogen concentration in human benign prostatic hyperplasia. Prostate 1982; 3:433–438.
34. Krieg M, Bartsch W, Thomsen M, Voigt KD. Androgens and estrogens: their interaction with stroma and epithelium of human benign prostatic hyperplasia and normal prostate. J Steroid Biochem 1983; 19:155–161.
35. Farnsworth WE. Roles of estrogen and SHBG in prostate physiology. Prostate 1996; 28:17–23.
36. Wernert A, Gerdes J, Loy V, et al. Investigations of the estrogen (ER-ICA test) and the progesterone receptor in the prostate and prostatic carcinoma on immunohistochemical basis. Virchows Arch A 1988; 412:387–391.
37. Schulze H, Claus S. Histologic localization of estrogen receptors in normal and diseased human prostates by immunocytochemistry. Prostate 1990; 16:331–343.
38. Kirschenbaum A, Ren M, Erenburg I, et al. Estrogen receptor messenger RNA expression in human benign prostatic hyperplasia: detection, localization and modulation with a long-acting gonadotropin-releasing hormone agonist. J Androl 1994; 15:528–533.
39. Rosner W. Estradiol causes rapid accumulation of c-AMP in human prostate. Proc Natl Acad Sci USA 1994; 91: 5402–5405.
40. Walsh PC, Wilson JD. The induction of prostatic hypertrophy in the dog with androstanediol. J Clin Invest 1976; 57:1093–1097.
41. Bruengger A, Bartsch G, Hollinger BE, et al. Smooth muscle cell of the canine prostate in spontaneous benign hyperplasia, steroid induced hyperplasia and estrogen or tamoxifen treated dogs. J Urol 1983; 130: 1208–1210.
42. Winter ML, Bosland MC, Wade DR, et al. Induction of benign prostatic hyperplasia in intact dogs by near-physiological levels of 5α-dihydrotestosterone and 17β-estradiol. Prostate 1995; 26:325–333.
43. Eckstein FMP, Zuckerman S. The effect of oestrogenic stimulation on the Mangabey prostate. J Anat 1944; 78:146.
44. Habenicht U-F, El Etreby MF. The periurethral zone of the prostate of the cynomolgos monkey is the most sensitive prostate part for estrogenic stimulus. Prostate 1988; 13:305–316.
45. de Voogt HJ, Rao BR, Geldof AA, et al. Androgen action blockade does not result in reduction in size but changes histology of the normal prostate. Prostate 1987; 11:305–311.
46. Levine AC, Kirschenbaum A, Droller M, Gabrilove JL. Effect of the addition of estrogen to medical castration on prostate size, symptoms, histology, and serum prostate specific antigen levels in four men with benign prostatic hypertrophy. J Urol 1991; 146:790–793.
47. Schweikart H-U, Tunn UW. Effects of the aromatase inhibitor testolactone on human benign prostatic hyperplasia. Steroids 1987; 50:1–3.
48. Gingell JC, Knonagel H, Kurth KH, Tunn UW. Placebo controlled double-blind study to test the efficacy of the aromatase inhibitor atamestane in patients with benign prostatic hyperplasia not requiring operation. The Schering 90.062 Study Group. J Urol 1995; 154:399–401.

Sarcoidosis



The cutaneous manifestations of sarcoidosis can vary greatly. Patients have presented with papules, nodules, plaques, ulcerations, and ichthyosiform lesions. Erythema nodosum is a well known complication of sarcoidosis. Annular lesions with elevated borders and central flattening are apparent in the patient shown.—*Stephen Kurtin, M.D., and Mark Lebwohl, M.D.*

Abstracts

*The following abstracts were presented by investigators at the Fourteenth Annual Research Day at Mount Sinai School of Medicine. Most of the investigators serve in the Samuel Bronfman Department of Medicine including those working at affiliated institutions such as the Bronx Veterans Affairs Medical Center, Elmhurst Hospital Center, Englewood, NJ, and Queens Hospital Center, Queens, NY. Five abstracts identified with an * were awarded special prizes and abstracts identified with an † were selected for oral presentation on Research Day. All others were presented as posters. Abstracts from Queens Hospital Center were presented as posters on Research Day held at that institution.*

Research in Medicine 1996
Mount Sinai School of Medicine

Alcohol Research

Elevated F_2-Isoprostanes Levels in Patients with Severe Alcoholic Liver Disease. S. I. Aleynik, M. A. Leo, M. K. Aleynik, and C. S. Lieber. Alcohol Research Center, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

F_2-Isoprostanes (F_2-IP) are peroxidation products of arachidonic acid considered to be the most reliable markers of endogenous *in vivo* lipid peroxidation, responsible, in part, for experimental alcoholic liver injury. Except for the hepatorenal syndrome. It is not known to what extent this mechanism pertains to man. Therefore, free and esterified plasma F_2-IP levels were measured by gas chromatography/mass spectrometry in 39 fasting subjects who underwent diagnostic percutaneous needle biopsy of the liver. Compared with six patients without fibrosis and only mild steatosis, F_2-IP levels were strikingly increased in nine individuals with alcoholic hepatitis (44.5 ± 5.9 vs 20.0 ± 1.7 pg/ml; $p < 0.001$). A similar increase was found in nine subjects with transition to, or with complete, alcoholic cirrhosis (40.4 ± 3.9; $p < 0.01$). However, in four patients with cirrhosis who were drinking heavily up to 24–48 hours before admission, F_2-IP levels were much lower (18.2 ± 0.82; $p < 0.05$). Similarly, 11 patients with early fibrosis (perivenular fibrosis) had no significant increase in F_2-IP. At the same time, esterified F_2-IP in plasma did not significantly change with fibrosis. Because F_2-IP are believed to be formed *in situ* on phospholipids and are subsequently released (to be esterified and excreted), the increase of F_2-IP we found could reflect decreased biliary excretion as a consequence of liver injury. This hypothesis is strengthened by the observation of a substantial excretion of F_2-IP in human bile as reported in an accompanying abstract (Leo et al.). On the other hand, the increased F_2-IP could result from enhanced lipid peroxidation associated with alcohol-induced liver injury. The reason for the lack of increase in recently drinking patients with cirrhosis is not fully understood, but may reflect the known capacity of ethanol to trap some radical species such as $OH^{\cdot}$. Hepatitis C associated with alcoholic liver disease did not appear to aggravate the increase in circulating F_2-IP.

In conclusion, although circulating esterified F_2-IP were found to be unchanged in patients with alcoholic liver disease, there was a remarkable increase in free F_2-IP, possibly reflecting enhanced hepatic lipid peroxidation as well as interference with biliary excretion and/or hepatic esterification.

Immunohistochemical and Western Blot Analysis of Cytochrome 1 P4502E1 Correlate in Formalin-Fixed Paraffin-Embedded Liver Samples. P. A. Cohen, K. M. Mak, I. Kessova, V. M. Mishin, T. Koivisto, A. S. Rosman, and C. S. Lieber. Alcohol Research Center, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

Cytochrome P4502E1 (2E1) is inducible by chronic ethanol consumption, and its increased activity results in activation of commonly used drugs (such as acetaminophen and anesthetics) to hepatotoxins. Therefore, assessment of hepatic 2E1 is needed for dosage adjustment in the management of alcoholic patients. However, current assessment of 2E1 requires either immunohistochemistry on frozen sections or Western blot (WB) analysis of tissue in excess of that needed for pathology. To obtain a more applicable method, we developed a procedure to detect 2E1 by immunohistochemistry in formalin-fixed, paraffin-embedded liver biopsies obtained routinely for diagnosis. Data were collected from rats fed ethanol-containing or control liquid diets for 3 weeks. Immunostaining was performed using antihuman rabbit 2E1 antibody as the primary antibody, and the immunoreaction was detected by the avidin-biotin immunoperoxidase method after treating sections with target-unmasking fluid, an antigen retrieval buffer which enhanced the staining of 2E1. In control rats, 2E1 staining was weak and perivenular. After ethanol feeding, it showed a lobular gradient, strongest perivenular and weakest periportal, similar to that seen on frozen sections. The staining intensity was scored as: 0 = no staining to 3 = strong staining. The zonal staining was scored as follows: 1 = perivenular zonal staining, 2 = midzonal, and 3 = panlobular. When the two scores were multiplied, a significant difference was found between alcohol-fed and control rats for both WB ($p < 0.0001$) and immunostaining ($p < 0.0001$) assessments. There was a corresponding increase of immunostaining scores and WB measurements of 2E1 content. Having established the usefulness of the immunohistochemical method, we validated this in 14 paraffin-embedded percutaneous human liver biopsies. In nonalcoholic liver, 2E1 staining was seen in the perivenular zone only, whereas the staining was perivenular to midzonal and sometimes periportal in samples of alcoholics. A significant correlation between the zonal staining scores ($p < 0.007$) or intensity × zonal staining scores and WB analysis were found ($p < 0.02$).

In summary, the immunohistochemical staining assessment correlated with WB analysis of hepatic 2E1 content. The lobular distribution of 2E1 in paraffin-embedded sections from alcoholic livers was consistent with that seen in frozen sections. We concluded that this procedure is useful for the assessment of 2E1 content in paraffin-embedded liver samples, thereby aiding in the management of heavy drinkers.

Ethnic Differences in Gastric Alcohol Dehydrogenase Isozyme Activities and Ethanol First-Pass Metabolism. K. Dohmen,[1] E. Baraona,[1] H. Ishibashi,[2] G. Pozzato,[3] C. Matsunaga,[4] K. Fujimoto,[4] and C. S. Lieber.[1] [1]Bronx VA Medical Center and Mount Sinai Medical School, New York, [2]First Department of Internal Medicine, Kyushu University, Fukuoka, Japan, [3]Inst. Med. Clin. Univ. of Trieste, Italy, [4]GI Div. Saga. Medical School, Japan.

A fraction of orally consumed alcohol does not reach the blood because of a gastric first-pass metabolism (FPM). The stomach has several alcohol dehydrogenase (ADH) isozymes, including one which is not expressed in the liver (σ-ADH), but their contribution to FPM is unknown. Based on previous findings that σ-ADH activity was markedly decreased in surgical samples of Japanese compared with non-Oriental patients, we assessed ADH activity in endoscopic gastric biopsies from 24 Japanese and 41 Caucasian men without gastric lesions or *Helicobacter pylori* infection. ADH isozyme activities were measured by starch gel electrophoresis and by comparing the typical activities of these isozymes: reduction of *m*-nitrobenzaldehyde (a preferred substrate of σ-ADH); reduction of acetaldehyde (a preferred substrate for γ-ADH); glutathione-dependent formaldehyde dehydrogenase (GDFD, a typical activity of χ-ADH). On electrophoresis, the intensity of the two σ-ADH bands of activity was lighter in Japanese than in Caucasian men ($p < 0.02$). This correlated with the *m*-nitrobenzaldehyde reduction ($p < 0.03$), which was also lower in Japanese than in Caucasian men ($p < 0.03$). By contrast, there were no ethnic differences in the reduction of acetaldehyde or in GDFD activity. To assess whether these differences in σ-ADH activity affect FPM, in 10 Japanese and 10 Caucasian healthy men, we quantified the amount of ethanol reaching the blood (using Michaelis-Menten analysis of blood levels) after oral and intravenous administrations of 0.3 g ethanol (as a 5% solution) per kg body weight, after a standard meal. FPM was much lower in Japanese than in Caucasian men ($p < 0.01$), despite the similar blood levels because Japanese men displayed a 2-fold faster elimination than Caucasian men ($p < 0.002$), because of their high prevalence of hepatic ADH2*2 polymorphism. By increasing the concentration of the imbibed ethanol to 40%, FPM increased in both groups to a comparable level, suggesting an additional contribution of the high K_m χ-ADH to gastric oxidation of high ethanol concentrations.

In conclusion: σ-ADH activity of normal gastric mucosa is lower in Japanese than in Caucasian men. This change is associated *in vivo* with decreased FPM, suggesting a significant contribution of this activity to ethanol oxidation in the human stomach. Potentially important is the possible impact of low σ-ADH activity on substrates involved in carcinogenesis.

F_2-Isoprostanes in Bile of Patients with Biliary Tract and Pancreatic Disorders. M. A. Leo, S. I. Aleynik, J. H. Siegel, F. Kasmin, M. K. Aleynik, and C. S. Lieber. Alcohol Research Center, Bronx VA and Beth Israel (North Division) Medical Centers and Mount Sinai School of Medicine, New York, NY.

F_2-Isoprostanes (F_2-IP) result from free radical-mediated peroxidation of arachidonic acid. They reflect *in vivo* lipid peroxidation and are present in human blood and liver. To determine whether they are excreted in human bile, esterified F_2-IP were measured by gas chromatography/mass spectrometry in bile collected during 31 endoscopic retrograde cholangio-pancreatographies (ERCP). In 11 subjects with normal ERCP (controls), bile contained significant amounts of F_2-IP (188 ± 27 pg/ml). In 10 individuals with bile duct stones, there was a 3-fold increase of F_2-IP (523 ± 129 pg/ml; $p < 0.05$). In 10 patients with pancreatic diseases (9 with chronic pancreatitis and 1 with a pancreatic mass) bile F_2-IP were also enhanced (545 ± 112 pg/ml; $p < 0.01$). These increases were significant even when the values were expressed per bile acids. Contrasting with the increase in F_2-IP, there was no significant change in α-tocopherol, the major physiological antioxidant. However, β-carotene was decreased in biliary tract and pancreatic diseases ($p < 0.05$) compared with controls. Results of liver function tests were normal except for bilirubin which was increased together with an increase in alkaline phosphatase. Total lipids, phospholipids, and cholesterol did not differ significantly in the three groups. One of the hypotheses proposed for the pathogenesis of chronic pancreatitis invokes excess production of free oxygen radicals. The present data provide the first evidence supporting such a mechanism in humans. In addition, it is possible that the striking increase in F_2-IP may contribute to lithogenesis in the bile. It is also noteworthy that the rise in F_2-IP was observed in the presence of a normal concentration of the antioxidant α-tocopherol and therefore probably reflects production in the liver and/or surrounding tissues.

In summary, substantial amounts of F_2-IP were detected in subjects with normal ERCP, and a significant rise was observed in pathological states, including chronic pancreatitis and biliary tract stones, documenting *in vivo* lipid peroxidation in these conditions. Such an increase could also play a lithogenic role in the bile.

Polyenylphosphatidylcholine Attenuates the Alcohol-Induced Fatty Liver and Hyperlipemia in Rats. K. P. Navder, E. Baraona, and C. S. Lieber. Alcohol Research Center, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

Chronic administration of polyenylphosphatidylcholine (PPC) (a soybean-derived lecithin, 40–52% of which is dilinoleoylphosphatidylcholine) prevents the development of cirrhosis in alcohol-fed baboons. However, it is unknown whether PPC also affects earlier changes induced by alcohol consumption, such as fatty liver. To assess this, 28 male rat littermates were pair-fed liquid diets containing 18% of energy as protein, 35% as fat, 11% as carbohydrate, and 36% either as ethanol or as additional carbohydrate for 21 days, and killed 90 min after intragastric administration of the corresponding diets. Half of them were given PPC (3 mg/diet calorie), whereas the other half received safflower oil, providing the same amount of linoleate. They consumed the same amount of alcohol (15.4 ± 0.5 g/kg/day). Compared with the pair-fed controls, both groups of alcohol-fed rats developed fatty liver (characterized by hepatomegaly and increased triglyceride and cholesterol ester concentrations). PPC did not alter total phospholipid concentration, but decreased concentrations of triglycerides (52.24 ± 10 mg/g liver vs 87.6 ± 7.1; $p < 0.01$ by analysis of variance) and cholesterol esters (1.65 ± 0.3 mg/g liver vs 3.05 ± 0.4; $p < 0.01$) in the alcohol-fed rats. These changes were even greater when expressed per total liver because PPC also attenuated the hepatomegaly (4.2 ± 0.1 g liver/100 g body weight vs 4.8 ± 0.2; $p < 0.01$). In addition, alcohol-fed rats developed hyperlipemia (characterized by postprandial hypertriglyceridemia and increased high-density lipoprotein (HDL)-cholesterol). PPC decreased the alcohol-induced increase in serum triglycerides (97.69 ± 6.8 mg/dl vs 196.4 ± 25.3; $p < 0.001$) and cholesterol in the very low density lipoprotein-low density lipoprotein (VLDL-LDL) fraction (28.66 ± 5.54 mg/dl vs 41.58 ± 3.76; $p < 02.05$), without affecting the increase in HDL-cholesterol, thereby decreasing further the atherogenic VLDL-LDL/HDL cholesterol ratio. By contrast, it did not affect either liver or serum lipids in the pair-fed controls. Moreover, PPC did not interfere with fat absorption nor alter plasma free fatty acids, which suggested that PPC acts by decreasing the derangements of fatty acid metabolism produced by ethanol in the liver.

In conclusion, PPC attenuates hepatomegaly, fatty liver and hyperlipemia (three prominent features of early alcoholic liver injury) without affecting the ethanol-induced increase in HDL-cholesterol. Thus, PPC decreases the alcohol-induced lipid disorders while maintaining the potential benefit of alcohol consumption on the development of atherosclerosis. These effects of PPC at the initial stages of alcoholic liver injury may prevent or delay the progression to more advanced forms of alcoholic liver disease.

Prevention of Hepatic Stellate Cell Activation by Dilinoleoylphosphatidylcholine. J. Poniachik, E. Baraona, and C. S. Lieber. Alcohol Research Center, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

Polyenylphosphatidylcholine (PPC) has been shown to protect against the development of fibrosis and cirrhosis in alcohol-fed baboons. The mechanism for this protective effect is unknown. Hepatic stellate cells (HSC) are transformed or "activated" to myofibroblast-like cells, which are engaged in the development of fibrosis. The *in vivo* protection by PPC is associated with a 2-fold reduction in the number of transformed cells, suggesting decreased HSC activation. The two major components of PPC are dilinoleoylphosphatidylcholine (DLPC) (approximately 50%) and palmitoyl-linoleoylphosphatidylcholine (PLPC) (approximately 24%). To study whether any of these major components of PPC affects activation directly, we assessed expression of α-smooth muscle actin (αSMA) and collagen synthesis (two recognized manifestations of activation) in primary HSC cultures. HSC were isolated from normal rat livers by density gradient centrifugation after digestion with pronase and collagenase; they were then seeded on uncoated plastic dishes and cultured for 8 to 12 days in four different media: a) Dulbecco's modified Eagle's medium with 20% bovine serum; b) the same medium with 17 mM ethanol, used as solvent for the phospholipids; c) medium containing 10 μM DLPC plus 17 mM ethanol; and d) medium containing 10 μM PLPC, also with 17 mM ethanol. After the HSC reached confluence, their expression of α-SMA was quantified by densitometry on Western blots, and their capacity to synthesize collagen was assessed by the 24-hour incorporation of [^{3}H]proline into collagen as well as by the percentage of newly secreted proteins as collagen. DLPC (but not PLPC) decreased α-SMA expression, as judged by a 3 to 4-fold reduction in densitometry units, compared with the other groups ($p <$ 0.05). DLPC also decreased by 40% the incorporation of [^{3}H]proline into collagen, compared with the effect of the vehicle alone or with that of PLPC ($p < 0.05$). The same trend was found for the percentage of proteins secreted as collagen.

In conclusion, DLPC decreases the *in vivo* activation of HSC, as judged by their expression of α-SMA and their capacity to synthesize collagen, whereas PLPC failed to show any effect. The reduction in the activation of HSC by DLPC may be responsible for, or at least contribute to, the prevention of fibrosis after PPC administration *in vivo*.

Ethanol Metabolism by Human Cytochromes P4502E1, P4501A2, and P4503A4. K. S. Salmela, I. B. Tsyrlov, I. G. Kessova, and C. S. Lieber. Alcohol Research Center, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

The microsomal ethanol-oxidizing system (MEOS) is dependent on the ethanol-inducible hepatic cytochrome P4502E1 (2E1); but, in addition, P4501A2 (1A2) has been shown to oxidize ethanol in rodents. In humans, the role of 1A2 has not been determined, although the involvement of cytochromes other than 2E1 has been suggested. Recently, rat cytochrome P4503A was also shown to have a common substrate with 2E1, namely chlorzoxazone. The aim of this study was to determine, whether, in addition to 2E1, two other human centrilobular P450s, 1A2 and P4503A4 (3A4), metabolize ethanol. In the presence of 0.1 mM azide (to inhibit contaminating catalase), ethanol (50 nM) oxidation by human recombinant 2E1, 1A2, and 3A4 (expressed in human hepatocyte-derived HepG2 cells) was 28 ± 4, 14 ± 2 and 7.5 ± 0.6 nmol/min/nmol P450, respectively (mean ± SEM). We found, however, that azide inhibits all three P450s studied, as shown by reduction in the metabolism of *p*-nitrophenol, methoxyresorufin, and benzoyloxyresorufin, specific substrates for 2E1, 1A2, and 3A4, respectively. Therefore, to assess ethanol oxidation by the recombinant P450s, we used specific inhibitors for each P450 in the absence of azide, namely 4-methylpyrazole (a 2E1 inhibitor), α-naphthoflavone (a 1A2 inhibitor), and troleandomycin (a 3A4 inhibitor). When calculated per P450 content, the methylpyrazole-sensitive part (16 ± 3 nmol/min/nmol 2E1) was less than half ($p < 0.05$) of the α-naphthoflavone-sensitive part (38 ± 4 nmol/min/nmol 1A2), whereas the troleandomycin-sensitive part was the smallest (9.2± 1.3 nmol/min/nmol 3A4). However, the catalytic efficiency (k_{cat}/K_m) of 2E1 was higher than that of 1A2 or 3A4 in the absence of azide. Specific inhibitors were also used to study the relative contribution of 2E1, 1A2 and 3A4 to MEOS in human liver microsomes. In samples obtained from patients with morbid obesity (hepatic steatosis) and organ donors (normal livers), MEOS activity displayed a similar sensitivity to 2E1 and 3A4 inhibition, whereas that of 1A2 was the smallest.

Conclusions: In addition to 2E1, 1A2 and 3A4 can also participate in hepatic ethanol oxidation. Therefore, 1A2 (inducible by smoking) and 3A4 (inducible by glucocorticoids) may also contribute to the liver pathology of the alcoholic patient, especially because heavy drinkers are commonly heavy smokers.

Antioxidant Effect of Dilinoleoylphosphatidylcholine with Protection against Lipid peroxidation and Cell Injury Produced by Arachidonate in Hepatoma Cells. U. Takeshige, M. A. Leo, S. Aleynik, M. Aleynik, and C. S. Lieber. Alcohol Research Center, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

Linoleic acid and other polyunsaturated lipids have been reported to promote liver injury, whereas we found that a linoleate-rich mixture of polyunsaturated phospholipids (PPC) protects against alcohol-induced fibrosis and cirrhosis in the baboon and CCl_4-induced cirrhosis in the rat while it opposes the oxidative stress generated by these toxins. To further study this paradox, we used an *in vitro* system with a Morris hepatoma cell line (RH7777). Generally, such tumor cells are resistant to peroxidation, unless enriched with arachidonate (AR). Thus, to promote lipid peroxidation, these cells were incubated with AR (100 μM), with or without 20 mM diinoleoylphosphatidylcholine (DLPC), the presumed active component of PPC. F_2-isoprostanes (F_2-IP) and 4-hydroxynonenal (4-HNE), parameters of lipid peroxidation, were measured by gas chromatography/mass spectrometry. AR increased cellular F_2l and 4-HNE (expressed per DNA) 42- and 6.2-fold, respectively ($p < 0.001$). This was associated with a striking exacerbation of cell death, observed microscopically and documented by a 2-fold decrease in cellular DNA and a 2- to 3-fold increase in the release of lactic dehydrogenase into the medium. By contrast, addition of DLPC to the AR significantly protected against lipid peroxidation, with a 71% and 36% reduction of F_2-IP and 4-HNE, respectively ($p < 0.001$). Injury to the cells was also reduced, as corroborated by a 78% decrease in the release of lactic dehydrogenase ($p < 0.001$). Thus, this study supports the role of DLPC as the active phosphatidylcholine species of PPC and demonstrates its antioxidant properties even in the presence of AR, a highly polyunsaturated fatty acid; it also illustrates that, in the presence of AR, RH7777 hepatoma cells provide a useful model for the assessment of putative protective agents against oxidative stress in the liver.

In conclusion, this study conducted *in vitro* under controlled conditions establishes the fact that, contrary to prevailing views, a polyunsaturated lipid, namely DLPC, acts as a potent antioxidant and protects hepatic cells against the oxidative stress induced by another polyunsaturated lipid, namely arachidonate. This *in vitro* evidence, added to the previously observed *in vivo* protection with DLPC-containing PPC, now provides a rationale for the clinical evaluation of DLPC in patients with liver diseases.

Inhibitory Effect of 3-Methylcholanthrene on Hepatic Microsomal Ethanol Inducible Cytochrome P4502E1 in Rats. I. B. Tsyrlov, K. S. Salmela, I. G. Kessova, and C. S. Lieber. Alcohol Research Center, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

Heavy drinking is commonly associated with smoking and clinically, synergistic effects have been described. This raises the possibility of potentiation or additive effects concerning the induction of the specific microsomal cytochromes P450 involved, namely P4502E1 (2E1) for drinking and P4501A2 (1A2) for smoking. Both 2E1 and 1A2 can sustain microsomal ethanol oxidation (MEOS). Therefore, these were studied after treatment of rats with ethanol and/or 3-methylcholanthrene (MC), a carcinogenic polycyclic hydrocarbon that mimicks smoking in terms of 1A2 induction. Contents of 2E1 and 1A2 were determined immunochemically in rats fed the Lieber-DeCarli liquid diet with 5% ethanol for 3 weeks and/or treated by MC (20 mg/kg) for the last 5 days. Kinetic parameters of MEOS activity were determined, with *p*-nitrophenol hydroxylation and 7-methoxyresorufin *O*-demethylation activities used as isozyme-specific reactions for 2E1 and 1A2, respectively. With microsomes of ethanol-induced rats, V_{max} of MEOS and 2E1 content were five and nine times higher, and the K_m was 2.5 times lower than in microsomes of control rats. With microsomes of MC-treated rats, V_{max} of MEOS and 1A2 content were increased 2- and 22-fold, respectively, whereas 2E1 content was 66% of control values, expressed per milligram of microsomal protein. In microsomes of ethanol-fed rats treated with MC, Lineweaver-Burk plots of MEOS revealed an overall V_{max} two times lower than in microsomes of ethanol-induced rats, with two-component kinetics of MEOS shown by Eadie-Hofstee plots. The 2E1 component had a K_m of 5.9 ± 0.5 mM (mean ± SEM), and a catalytic efficiency value (k_{cat}/K_m) of 15.4 ± 1.9 mM^{-1} min^{-1}. For the 1A2-component, the values were 14.6 ± 3.5 and 1.08 ± 0.2, respectively. Combined treatment with ethanol and MC led to a 27-fold increase of 1A2 but a 5.4-fold decrease of 2E1 content, compared with microsomes of ethanol-treated rats.

Summary: Combined treatment of rats with ethanol and MC results in a significant reduction of the induction of 2E1 by ethanol even when the latter is consumed in amounts that, by themselves, are sufficient to cause a striking induction. Despite its low catalytic efficiency, 1A2 contributed to MEOS when induced by MC either with or without ethanol. We conclude, therefore, that in terms of 2E1 induction by ethanol, a net effect of MC is inhibitory rather than synergistic.

Cardiology

***Platelet-Derived Growth Factor-Specific Regulation of the *JE* Promoter in Rat Aortic Smooth Muscle Cells.** V. Y. Bogdanov, M. Poon, and M. B. Taubman. Divisions of Cardiology and Molecular Medicine, Mount Sinai School of Medicine, New York, NY.

JE is a member of the family of "immediate-early" genes induced by growth factors and cytokines. *JE* encodes a low molecular weight secretory glycoprotein analogous to the human monocyte chemoattractant protein-1 (MCP-1). *JE* and MCP-1 proteins are thought to play an important role in the inflammation and in the recruitment of monocyte/macrophages to the vessel wall during the development of atherosclerosis. Using a luciferase reporter system and transient transfection assays of rat aortic smooth muscle cells (SMC), we identified a region of the proximal rat *JE* promoter which is responsive to platelet-derived growth factor (PDGF), but not to other growth factors (angiotensin II, α-thrombin, basic fibroblast growth factor, or such cytokines as interleukin 1-β and tumor necrosis factor-α). The full response to PDGF (~-6-fold) requires the cooperative activity of two potentially novel *cis*-acting elements, at positions −146 to −128 (element 1) and −84 to −59 (element 2). These elements bind different protein fractions in electromobility shift assays (EMSA). Element 1 binds a protein fraction within 15 minutes of treatment with PDGF, but not with angiotensin II, an agent which is hypertrophic for SMC, rather than hyperplastic. This protein fraction remains bound 1 hour after treatment. Element 2 also binds a protein fraction in response to PDGF, but not angiotensin II. The binding of this fraction is transient and is gone within 1 hour. Identification of the proteins bound by elements 1 and 2 may provide insights into PDGF-specific responses in vascular SMC and to differences in signaling accompanying hyperplastic (PDGF) versus hypertrophic (angiotensin II) growth.

†Relationship of Angiotensinogen Polymorphism with Office and Ambulatory Blood Pressure. A. G. Gharavi, M. S. Lipkowitz, J. A. Diamond, R. Chamie, A. R. Travis, and R. A. Phillips. Mount Sinai School of Medicine, New York, NY.

Several but not all studies have shown that M235T polymorphism of the angiotensinogen (AGT) gene is associated with hypertension. Using 24-hour ambulatory blood pressure (24hr-ABP) monitoring, we studied the relationship between the M235T polymorphism and hypertension in nonblack subjects referred for evaluation of office BP > 140/90 mm Hg. Subjects (M = 33; F = 17) were studied off treatment with 2-D guided M-mode echocardiography and 24hr-ABP monitoring. The M235T genotypes were identified after *BSTUI* digestion of leukocyte DNA amplified by the polymerase chain reaction. Frequencies of the M and T alleles were 0.44 and 0.56, respectively. Age, body mass index, gender distribution, and LV mass (Penn) were similar between genotype groups. Based on office BP, the TT genotype could not be differentiated from the MM genotype. However, the 24hr-ABP, the TT genotype was clearly associated with higher BP than both MM and MT genotypes. This difference remained significant after adjustment for age, gender, and body mass index.

	MM	MT	TT
N	11	22	17
Age	44 ± 9	45 ± 13	46 ± 11
BMI	27.8 ± 2.3	26.1 ± 7	26.8 ± 2.9
Office BP	150/97 ± 25/13	147/95 ± 23/13	161/104 ± 25/15*
24 hr-ABP	138/88 ± 10/09	141/89 ± 15/111	152/97 ± 18/12**
LV mass (gm/m^2)	103 ± 24	88 ± 19	98 ± 24

* $p < 0.02$ vs MT; ** $p < 0.05$ vs MT and MM (ANOVA).

A *post hoc* power analysis revealed that, in our sample size, office measurements had a 29% power to detect a >10 mm Hg difference in systolic BP between genotype groups, whereas ambulatory measurements had a 72% power to detect the same difference. Hence, ambulatory monitoring improved the analytic power of our study and allowed detection of a clear and consistent relationship between angiotensinogen polymorphism and hypertension with a relatively small sample size.

Thrombotic and Complex Coronary Lesions Correlate with More Severe/Acute Clinical Presentation of Unstable Angina. G. Dangas, R. Mehran, V. Kakarala, S. Wallenstein, and J. A. Ambrose. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Unstable angina (UA) is usually related to acute thrombosis superimposed on a disrupted plaque. At the same time, significant clinical diversity exists. We hypothesized that intracoronary thrombus (ICT) determines the severity of the clinical presentation of UA. Since angiography is sensitive only for large amount of ICT, this finding should correlate with the highest clinical UA severity (Braunwald classes III = rest angina within 48 hours, C = post-myocardial infarction, and c = refractory to maximal medical therapy).

Methods: We conducted a prospective study of 284 patients with UA who underwent cardiac catheterization. A single angiographer, blinded to the clinical classification, interpreted all angiograms. Culprit lesions identified in 200 patients were classified according to ICT, complex lesions (Ambrose classification), and scaled in accord with the TIMI study. We performed univariate and multivariate logistic regression analysis of the angiographic findings controlling for all cardiac risk factors, before percutaneous transluminal coronary angioplasty or coronary artery bypass graft and multivessel disease and we sequentially compared Braunwald classes III, C, c to classes <III <C, <c.

Results: Complex lesions doubled the likelihood for class III (odds ratio [OR] = 2, 95% confidence interval [CI] = 1–4, $p = 0.04$). ICT increased 6-fold the likelihood of class C (OR = 6, CI = 2–19, $p = 0.005$) and 3-fold the incidence of class c (OR = 3, CI = 1–7, $p = 0.02$). TIMI-flow <3 increased 4-fold the presence of class C (OR = 4, CI = 1–12 $p = 0.03$). Detection of ICT increased 7-fold with class C presentation (OR = 7, CI = 2–24, $p < 0.001$) and 3-fold with class c (OR = 3, CI = 1–8, $p = 0.01$).

Conclusion: Angiographically detected ICT, decreased TIMI-flow, and complex lesions are strongly associated with the most severe/refractory UA cases.

Endothelial Function after Coronary Angioplasty in Pigs. F. Fonseca,[1] M. Izan,[1] A. Padurean,[1] R. Gallo,[1] N. Rienz,[2] E. Schachter,[2] J. Fallon,[1] J. Chesebro,[1] V. Fuster,[1] J. Badimon.[1] Cardiovascular Institute[1] and Pulmonary Division,[2] Mount Sinai School of Medicine, New York, NY.

Although abnormal vasoreactivity after arterial injury seems related to endothelial damage, its evolution during the healing process is not known. *In vivo* and *in vitro* vasoreactivity were assessed after severe coronary injury induced by balloon angioplasty (BA) in Yorkshire albino pigs ($n = 30$). *In vivo* coronary vasoreactivity to dextrose (vehicle control), bradykinin (BK), and serotonin (5-HT) (endothelium-dependent agonists), as well as nitroglycerin (NTG) (endothelium-independent substance) was examined at different times after BA (ranging from 0 to 12 weeks). Percent changes in coronary diameter at the site of BA were determined from coronary angiography before and immediately after each agonist infusion using nonionic contrast medium in the same phase of the cardiac cycle. *In vitro* studies of vasoresponses in isolated coronary rings to BK, 5-HT, and NTG were measured in parallel with *in vitro* experiments. Relaxation was expressed as the percent change from the tension of tissue contracted by prostaglandin F2α. *In vivo* studies showed acute impairment of vasoreactivity for all agonists after BA. Endothelium-dependent vasoresponses returned to normal as early as 4 weeks after BA. Endothelium-independent relaxation elicited by NTG was normal just 1 week after BA. *In vitro* studies showed that endothelial dysfunction was present (maximal relaxation <50%) with both BK and 5-HT for long as 12 weeks after BA, but the relaxation to NTG was normal throughout the study. Immunohistochemical analysis using Dolichos Biflorus Agglutinin (DBA) revealed endothelial coverage from 4 weeks after BA. Our results suggest that in spite of endothelial regeneration, endothelial dysfunction is still observed for up to 12 weeks after BA and that *in vitro* studies seem to be more sensitive for the characterization of this damage.

Heparin and Glycoprotein IIb/IIIa Receptor Blockade Does Not Reduce Thrombus Growth More Than Heparin Alone. R. Hayes, J. Badimon, B. Coller, S. Sharma, S. Duvvuri, J. Marmur, J. Fallon, V. Fuster, and J. Chesebro. Divisions of Cardiology, and Hematology, Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Platelet glycoprotein (GP) IIb/IIIa receptor blockade with c7E3 plus heparin and aspirin reduces clinical events in patients; however, the addition of heparin appears to increase major bleeding. Thus, we tested whether c7E3 alone would decrease thrombus growth, as well as c7E3 plus heparin (vs control [Aspirin (ASA), 325 mg]). Arterial blood from patients undergoing percutaneous transluminal coronary angioplasty (PTCA) was perfused over severely injured arterial wall in the Badimon perfusion chamber for 5 minutes at rheological conditions typical of a mildly stenotic coronary artery (1690/s). Blood was perfused at baseline (control), 10 minutes after c7E3 alone (0.25 μg/kg bolus + 10 μg/min infusion) which abolished platelet aggregation and produced >80% receptor blockade, and 6 hours after PTCA in the presence of c7E3 and heparin (70 U/kg bolus + 600–1000 U/hr infusion) (aPTT >60 s). Thrombus area (TA) was analyzed by planimetry.

The results show that c7E3 alone reduces thrombus formation as much as c7E3 plus heparin on injured arterial wall. Although heparin's anticoagulant effects may still be of value, they do not further reduce platelet thrombus growth in the presence of high-grade GP IIb/IIIa receptor blockade.

TABLE

Treatment Group	TA (μm^2)[a]	ΔTA[b]	% Receptor Blockade
Control ($n = 12$)	11001 ± 813	–	0
c7E3 ($n = 8$)	4935 ± 659*	47	91 ± 2
C7E3/Heparin ($n = 10$)	6521 ± 857*	57	90 ± 6

[a] Results are expressed as x ± SEM.

[b] ΔTA = % reduction in thrombus area versus control.

* $p < 0.0001$ vs control.

Demonstration of a Circulating Anti-prostacyclin Receptor Antibody. N. Kahn, W. Bauman, R. Zhang, and A. Sinha. Department of Medicine, Mount Sinai School of Medicine, New York, and Bronx VA Medical Center, Bronx, NY.

The prevalence of premature coronary artery disease (CAD) is increased in individuals with chronic spinal cord injury (SCI). The underlying mechanism for this increased prevalence remains obscure. Because prostacyclin (PGI_2), through its inhibitory effect on platelet aggregation, is known to play an important role in the prevention of CAD, we investigated the interaction between platelets and PGI_2 in those with SCI. Incubation of normal, nonSCI platelets in SCI plasma ($n = 12$) resulted in the loss of high-affinity binding of PGI_2 to platelets, determined by using $^3H\text{-}PGE_1$ as a stable probe. The loss of high-affinity PGI_2 binding ($Kd_1 = 9$ nM), led to the failure of PGI_2 to inhibit the platelet-stimulated thrombin generation. The increase of cellular cyclic AMP level mediated through the binding of PGI_2 to low-affinity receptors in platelets ($Kd_2 = 0.9$ mM) was unaffected in SCI platelets. Polyacrylamide gel electrophoresis (PAGE) and immunoblot of SCI plasma showed the presence of an IgG band, which specifically blocked the binding of $^3H\text{-}GE_1$ to the high-affinity PGI_2 receptors of normal platelets. PAGE of the reduced IgG band, the amino acid sequence of the novel band as a heavy chain of IgG, which inhibits the binding of $^3H\text{-}GE_1$ to the high-affinity platelet PGI_2 receptors, strongly suggested the presence of an antibody to the prostacyclin receptor in SCI plasma that was responsible for the inhibition of high-affinity PGI_2 binding to platelets.

Lipid and Lipoprotein Metabolism in Pancreatic Carboxyl Ester Lipase Gene Knockout Mice. L. Li, W. Weng, A. M. van Bennekum, W. S. Blaner, J. Breslow, and E. A. Fisher. Cardiovascular Institute and Department of Medicine, Mount Sinai School of Medicine and Rockefeller University, New York, NY.

Pancreatic carboxyl ester lipase (CEL) hydrolyzes *in vitro* cholesteryl esters (CE), retinyl esters (RE), triglycerides (TG), and lysophospholipids (lysoPC). It is also a major component of breast milk in many mammals, including humans. In the intestine, it is thought to liberate free cholesterol (FC) and retinol from their esters in preparation for absorption. Results from *in vitro* and *in vivo* studies, however, have suggested several other roles for CEL in lipid and lipoprotein metabolism, some of which are controversial. The CEL gene knockout (CK) mice were generated to better elucidate the physiological functions of CEL. CK mice are born in normal-sized litters, appear healthy, and grow normally. Pancreatic and breast-milk CEL activities were abolished completely in CK (−/−) mice. In intestinal cholesterol absorption tests, neither −/− nor +/+ littermate controls absorbed nonhydrolyzable cholesteryl ether. CK mice also did not show significant differences in FC absorption (80% ± 21%, mean ± SD) compared with +/+ (76% ± 6%). With CE, −/− mice absorbed about 50% of CE as +/+, suggesting another enzyme may have hydrolyzed CE. There was no evidence for a bacterial enzyme, because sterilization of intestinal microbial flora had no effects on CE absorption. Surprisingly, for RE, −/− mice had the same absorption efficiency as +/+. The responses to different diets (mouse chow diet, Western-type high-fat diet, and atherogenic diet) were similar in −/− and +/+ mice in terms of plasma concentrations of total cholesterol (C), high-density lipoprotein-C, TG, fast-performance liquid chromatography-lipoprotien profiles, and ratios of free to total C and of lysoPC to phosphatidylcholine. Our results indicate CEL may have several redundant functions in lipid and lipoprotein, with significant effects observed only for intestinal CE processing. Because CEL has the potential to modify structural features of lipoproteins and reduce lysoPC content of oxidized low-density lipoprotein, we are investigating effects of CEL expression atherogenesis in our mouse lines.

Involvement of the Proteasome in the Degradation of Presecretory Apolipoprotein B, The Major Protein of Low-Density Lipoproteins. D. Mitchell, H. Wang, and E. A. Fisher. Cardiovascular Institute and Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Apolipoprotein B (apoB) is the major protein of low-density lipoproteins and its plasma level is a strong risk factor for coronary artery disease. The major source of apoB is the liver; its net output is determined by its rate of degradation. ApoB degradation increases when there is insufficient lipid available for the assembly of a lipoprotein, as in the genetic disease, abetalipoproteinemia. Little is known about the degradative process. A model to study apoB degradation has been human hepatocarcinoma cells (HepG2) maintained in the absence of fatty acids to create a state of lipid insufficiency. To test whether apoB can be a substrate for the proteasome, which degrades cytosolic proteins, specific inhibitors of its proteolytic activity (MG132, a peptidyl aldehyde, and lactacystin, which covalently links to the catalytic site) were tested in fatty acid-deprived HepG2 cells. At time 0, ^{35}S-methionine and inhibitor in buffer or buffer alone (control) were added to wells of cultured cells. Two hours later cell lysate and conditioned medium were taken for immunoprecipitation analysis. ApoB degradation was strongly inhibited by either compound, as manifested by increased recovery versus control of radiolabeled apoB, which averaged for MG132 and lactacystin, respectively, 3.3 ± 0.1 and 2.8 ± 0.3 (fold increases of lysate + medium apoB, mean ± SE; $n = 11$ [MG132] or 6 [lactacystin]; $p < 0.001$ for either). The "rescued" apoB was mainly in the cell lysate; this was confirmed by immunofluorescence studies. In contrast, if oleic acid was added at time 0, a significant fraction of apoB was then secreted complexed with lipids, consistent with reports that when lipidation of apoB is blocked, its translocation across the endoplasmic reticulum membrane and ultimate secretion are arrested. Our results imply that a translocational arrest of apoB can result in the exposure of domains to the cytosol, allowing the targeting of a protein initially intended for secretion to destruction by the proteasome.

Monocyte Chemoattractant Protein-1 Induces Tissue Factor in Human Aortic Smooth Muscle Cells. A. D. Schecter, B. Rollins, J. T. Fallon, M. Rossikhina, Y. Nemerson, and M. B. Taubman. Divisions of Cardiology and Thrombosis and the Department of Pathology, Mount Sinai School of Medicine, New York, NY, and the Harvard Medical School, Boston, MA.

Tissue factor (TF), a transmembrane glycoprotein that initiates the coagulation cascade, is present in human atherosclerotic plaques and is induced in smooth muscle cells (SMC) in experimental arterial injury. Monocyte chemoattractant protein-1 (MCP-1) is involved in the recruitment of monocytes to the atherosclerotic plaque. Like TF, MCP-1 is found in the plaque and in arterial media after injury. We now demonstrate that MCP-1, in addition to being a chemoattractant, induces TF in SMC and monocytes and may thus link the inflammatory and thrombotic components of atherosclerosis. Although quiescent SMC had undetectable levels of TF mRNA, human rMCP-1 (0.1 ng/ml) markedly increased mRNA levels to 6 hours after treatment. The induction of TF mRNA by MCP-1 was accompanied by an accumulation of TF protein in the SMC. Competitive binding studies with radiolabeled MCP-1 demonstrated high levels of an MCP-1 receptor (40,000 binding sites/cell) with a K_d of 1.7 ± 0.02 nM by Scatchard analysis. This K_d is similar to that obtained for MCP-1 receptors (CC-CKR-2A and B) recently cloned from human monocytes. RNA blot analyses with CC-CKR-2 cDNA and reverse transcriptase polymerase chain reaction with specific primers to the cloned receptors were negative demonstrating that the SMC possess a different MCP-1 receptor. To examine MCP-1 signaling, SMC were pretreated for 24 hours with phorbol 12, 13-dibutyrate to down-regulate protein kinase C (PKC) activity. This blocked induction of TF mRNA and protein by MCP-1 but not by platelet-derived growth factor (PDGF). Staurosporine, a direct PKC inhibitor, also inhibited the induction of TF by MCP-1, but not by PDGF. To study the role of calcium mobilization, SMC were treated with MCP-1 and BAPTA/AM, an intracellular calcium chelator. This blocked induction of TF by both MCP-1 and PDGF. In conclusion, the induction of TF by MCP-1 depends on direct activation of PKC supporting MCP-1 signaling via a phosholipase C-dependent pathway and intracellular calcium.

Sagittal Abdominal Diameter/Thigh Circumference and Waist Hip Ratio Highly Correlated. D. A. Smith, E. Ness, R. Herbert, C. Schecter, R. Phillips, J. Diamond, and P. Landrigan. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

In a prevalence study of coronary heart disease (CHD) in 526 Triboro Bridge and Tunnel Authority (TBTA) workers, sagittal abdominal diameter (height of stomach in reclining position) divided by circumference of thigh (10 cm above suprapatellar border) (SAD/thigh) was measured as were the waist-to-hip ratio (WHR), body mass index (BMI), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), apolipoproteins A and B (Apo A, Apo B), casual glucose, averaged sitting 2nd and 3rd systolic and diastolic blood pressures (sBP, dBP) and uric acid (urate), all variables often correlated with insulin sensitivity/resistance. BMI, WHR, and SAD/thigh were significantly correlated with all of these variables. For most variables WHR and SAD/thigh had similar Pearson correlation coefficients and appeared to be slightly better correlates of urate, sBP, glucose, apolipoprotein B, and TG than BMI. These findings suggest that SAD/thigh is equally as a good measure of central obesity as WHR, and it may be a more simple and practical measure.

	Pearson Correlation Coefficients (p values)				
	BMI	WHR	SAD/thigh	TG	Apo B
BMI	1.0	0.55 (0.000)	0.43 (0.000)	0.09 (0.052)	.15 (0.001)
WHR	–	1.0	0.74 (0.000)	0.26 (0.000)	0.32 (0.000)
SAD/thigh	–	–	1.0	0.25 (0.000)	0.30 (0.000)

	Pearson Correlation Coefficients (p values)					
	Apo A	HDL-C	Gluc	sBP	dBP	Urate
BMI	−0.16 (0.000)	−0..22 (0.000)	0.07 (0.000)	0.19 (0.000)	0.22 (0.000)	0.26 (0.000)
WHR	−0.22 (0.000)	−0.37 (0.000)	0.22 (0.000)	0.24 (0.000)	0.24 (0.000)	0.37 (0.000)
SAD/thigh	−0.10 (0.03)	−0.26 (0.000)	0.21 (0.000)	0.29 (0.000)	0.28 (0.000)	0.35 (0.000)

The Puzzling Positivity of Thallium Scan and Negativity of Exercise Electrocardiogram: "Ischemic ST-Segment Counterpoise" as a Concept and a Determinant. C. Tziros, M. Khan, B. Manyam, I. Gujral, and J. Madias. Division of Cardiology, Elmhurst Hospital, New York, NY.

The puzzling occurrence of a falsely negative exercise electrocardiogram (ECG−) in association with a thallium-201 myocardial scintigraphy (Tl) showing reversible ischemia (RI) is well appreciated. Various correlates of this phenomenon have been described in the past, i.e., one-vessel disease, low work load or inadequate chronotropic response, previous myocardial infarction, or baseline ECG abnormalities. Our objective was to test the hypothesis that ST-segment ECG forces generated by RI from territories opposite each other (TOEO) may result in a ECG− ("ischemic ST-segment counterpoise" [ISTC]). We studied 104 patients with RI on Tl: 62 had a ECG− at ≥85% of the maximal predicted heart rate, and 42 had a positive ECG (ECG+). Stress SPECT Tl polar maps were divided into four equal sectors [anterior (A), posterior (P), septal (S), and lateral (L)], and the mean relative count rates (CR) from these sectors were used to calculate the A/P or P/A and the S/L or L/S ratios, with the lower CR entered as a numerator; the smaller of these two ratios was used as an index of the greatest difference in the perfusion of two TOEO. This variable had a value of 0.81 ± 0.06 ($\bar{x}$ ± SD) for the patients with ECG− and 0.71 ± 0.09 for the patients with ECG+ ($p = 0.0005$), indicating that the patients with balanced TOEO, manifesting ISTC, tend to have a ECG−.

Thus, ISTC in patients with RI appears to be a determinant of a false ECG response to exercise; consequently an exercise test based only on the ECG may not be an adequate diagnostic aid, particularly for patients with RI in multiple heart territories (a situation often not known or suspected beforehand).

Dermatology

†Henoch-Schonlein Purpura Induced by Ciprofloxacin. A. Sapadin, P. Calderon, D. Rudikoff, R. Phelps, and M. Lebwohl. Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

Since its introduction in 1983, ciprofloxacin has been widely used as an antibacterial agent for infection of the urinary tract, gastrointestinal tract, bone, and soft tissues. Adverse effects primarily involve the gastrointestinal tract and occur in approximately 5 to 10% of patients who are treated with this drug. Henoch-Schonlein purpura (HSP) is a vasculitic syndrome characterized by disease of the skin, joints, gastrointestinal tract, and kidneys. Although it is more prevalent in the pediatric population, it may occur at any age. Herein we describe a case of ciprofloxacin-induced adult HSP. Only one such case has been reported in the literature, although a wide variety of drugs have been previously incriminated. The patient was a 64-year-old man with a history of alcoholic cirrhosis for whom ciprofloxacin had been prescribed for a diarrheal illness of presumed infectious etiology. He was receiving no other medications and had no evidence of any other infection at that time. After initially discontinuing ciprofloxacin for several days the patient reinstituted therapy and then developed fever, polyarticular arthralgias, abdominal pain, and a cutaneous eruption. Skin examination was significant for palpable purpura and petechiae distributed on the distal extremities. Laboratory tests revealed an elevated blood urea nitrogen (67 mg/dL) and creatine (4.0 mg/dL) and microscopic hematuria. Histopathology of a recent papular lesion demonstrated the classic features of leukocytoclastic vasculitis. Direct immunofluorescence revealed a granular pattern of IgA deposition surrounding superficial dermal vessels, a characteristic finding in HSP. The patient was treated with prednisone (1 mg/kg/day). The symptoms abated, purpura cleared, and renal function normalized within 1 week without subsequent relapse. Although it is often difficult to establish a causal relationship between administration of a drug and a subsequent reaction, the temporal relationship with the ingestion of this quinolone implicates ciprofloxacin as the most likely etiologic agent. Clinicians should be alerted to the possibility of HSP when prescribing such a widely used drug.

Disseminated Cryptococcosis Mimicking Cutaneous Necrotizing Venulitis. A. Sapadin,[1] E. J. Bottone,[2] R. Phelps,[1] M. Gordon,[1] and M. Lebowhl.[1] Department of Dermatology[1] and Division of Infectious Diseases,[2] Mount Sinai School of Medicine, New York, NY.

Disseminated cryptococcosis is a life-threatening infection with cutaneous involvement in 10 to 15% of cases. The cutaneous manifestations are protean and nonspecific. Morphologic findings include papules, pustules, ulcerated nodules, cellulitis, molluscum- herpes simplex-, Kaposi's sarcoma-, or pyoderma gangrenosum-like lesions. Lesions resembling cutaneous necrotizing venulitis of the lower extremities, herein described, have not been previously reported. The patient, a 62-year-old Caucasian women, was hospitalized 3 weeks after orthotopic liver transplantation when a biopsy revealed severe rejection. Medications taken before admission included Prograf (FK 506) and prednisone. OKT3 immunosuppressive therapy was initiated 1 week after admission. The patient developed low-grade fevers, headaches, and mental status changes characterized by a waxing and waning course. Intravenous gancyclovir therapy was initiated for presumed cytomegalovirus infection. Chest x-ray demonstrated a nodular density with a central lucency in the right lower lung field. The patient was noted to have palpable purpura of the lower extremities, most prominent around the ankles. A punch biopsy and skin scraping of the right lower extremity demonstrated multiple encapsulated yeast forms with minimal inflammatory reaction. The serum cryptococcal antigen titer was 1:4096 and the cerebrospinal fluid (CSF) titer was 1:1024. *Cryptococcus neoformans* was isolated from skin, blood, and CSF cultures. Despite aggressive antimycotic therapy that included amphotericin-B, fluconazole, and flucytosine, the patient died approximately 2 weeks later. This case emphasizes that cutaneous necrotizing venulitis may be included among the varied clinical presentations of cutaneous cryptococcosis. The vascular eruption of the former most often appears on the lower extremities and palpable purpura is its signature. Early performance of skin biopsy and scraping in an immunocompromised host is advocated when this diagnosis is suspected.

Immunofluorescence Analysis of the Fibrillins in Pseudoxanthoma Elasticum Skin and in an *in Vitro* Three-Dimensional Culture Model. A. Sapadin, E. Schwartz, S. Truter, J. Rosenbaum, and M. Lebwohl. Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

Pseudoxanthoma elasticum (PXE) is a heritable connective tissue disease involving altered elastic fiber formation. Among the components of the elastic fibers are elastin and elastin-associated microfibrils. Although the complete inventory of macromolecular constituents of elastin-associated microfibrils is presently unknown, two microfibrillar proteins, fibrillin-1 (Fbn-1) and fibrillin-2 (Fbn-2) have recently been localized to them. The aim of this study was to use indirect immunofluoresence to identify the presence and distribution of these proteins in adult skin and in the matrix of fibroblasts grown on a nylon mesh culture model. The fluorescence intensity of each mesh sample was determined by means of a Zeis Axiovert fluorescence microscope. Fluorescence images were recorded with a slow-scan, cooled CAD camera. Lesional PXE skin demonstrated no unexpected abnormality when compared with normal skin. The typical candelabra pattern of Fbn-1 staining in the papillary dermis was preserved in PXE skin. Staining for Fbn-2 was not appreciably present in either normal or PXE skins. In contrast, immunostaining of sections of the nylon mesh model for PXE and normal samples demonstrated a fibrillar pattern for both Fbn-1 and Fbn-2. Further, whereas the intensity of staining for Fbn-1 was comparable between the PXE and normal samples, fluorescence of Fbn-2 appeared significantly attenuated in the PXE sections. We conclude that Fbn-2 is present in the extracellular matrix of adult human fibroblasts and may be implicated as a candidate gene in PXE.

Increased Expression of β1-Integrin Receptor in UVB and Tretinoin-Treated Hairless Mouse Skin. A. Sapadin,[1] L. H. Kligman,[2] and E. Schwartz.[1] Department of Dermatology, Mount Sinai School of Medicine,[1] New York, NY and University of Pennsylvania,[2] Philadelphia, PA.

Chronically sun-damaged skin is characterized by alterations to the dermal extracellular matrix. Integrins (heterodimeric glycoproteins composed α and β subunits) are cell surface receptors that serve to transduce extracellular stimuli such as UV into intracellular signaling. The aim of this study was to determine if integrin expression is altered by UVB and tretinoin treatment. Hairless mice were irradiated thrice weekly for 10 weeks with UVB. In the 10-week postirradiation period, mice were treated topically five times per week with tretinoin

(0.05%) or the water-propylene glycol vehicle. Antibodies specific for the β1-integrin chain were used with indirect immunofluorescence microscopy. In the untreated skin the β1-integrin was localized predominantly in the basal layer of the epidermis with only sparse reactivity in the dermis. In contrast, the dermis of UVB-treated skin showed clumped focal areas of β1-integrin expression with suprabasal and basal localizations in the epidermis. Tretinoin-treated skin displayed a complex reticulated pattern of β1-integrin expression throughout the dermis. Confocal microscopy revealed extensive staining with punctate cell surface localization. Suprabasal and basal expression was present in the epidermis. These results suggest that UVB treatment increases the dermal expression of β1-integrin. Tretinoin led to the formation of an extensive cell-matrix network. These connections may function to stabilize the dermal structure and may be important in mediating the ability of tretinoin to repair UV-damaged skin.

Increased Expression of Type I Collagen in Cultured Fibroblasts of White Fibrous Papulosis Patients. A. Sapadin, S. Truter, J. Rosenbaum, E. D. MacDonald, A. Persaud, and M. Lebwohl. Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

White fibrous papulosis of the neck (WFP) is a recently described entity characterized by asymptomatic, multiple, small, white, firm papules localized on the neck in elderly persons. Its etiology and pathogenesis have not yet been elucidated. The only consistent finding on histopathologic examination is thickened collagen bundles in the dermis. Paucity of elastic fibers has been observed in some, but not all patients, particularly in the papillary dermis. Using standard immunofluorescence techniques we have previously demonstrated that type III collagen is present in the dermis in a highly organized pattern and appears to encircle bundles of type I collagen. Further, fibrillin-1 is present at the dermal-epidermal junction (DEJ) with characteristic "skip" areas, i.e., intermittent disruptions of the normal candelabra pattern seen at this location. Additional studies with confocal laser microscopy have supported these findings. The aim of the present study was to use Northern blot analysis to determine whether collagen type I expression was increased in cultured lesional WFP fibroblasts. The results indicated an approximate 2-fold increased expression of collagen type I mRNA for cultured WFP fibroblasts. Increased expression of this protein may contribute to the indurative appearance of the lesional skin in these patients.

Lichen Planus Pemphigoides in the Absence of Clinically Apparent Bullae with a Predominantly Unilateral Distribution. A. Sapadin,[1] I. Kanton,[1] R. Phelps,[1,2] I. S. Schwartz,[2] and M. Lebwohl.[1] Departments of Dermatology[1] and Pathology,[2] Mount Sinai School of Medicine, New York, NY.

Lichen planus pemphigoides (LPP) is a rare disease in which blistering occurs in association with lesions of classic lichen planus (LP). In most reported cases lesions of LP are distributed bilaterally, and are accompanied or followed by blistering with histopathologic and direct immunofluorescence (DIF) criteria of bullous pemphigoid (BP). Our patient, a 44-year-old Pakistani woman, had an 8-year history of hypothyroidism and was treated with levothyroxine. She awoke one morning with a right-sided lichenoid eruption involving the intertriginous areas, right arm, and right lower trunk. Many of the intertriginous lesions appeared as dark brown patches and were consistent with postinflammatory hyperpigmentation. The lesions on the right arm appeared as a linear grouping of glistening, violaceous, flat-topped papules, a typical appearance of linear or Koebnerized lichen planus. No blisters were apparent. Routine bloodwork was noncontributory. Hepatitis C antibody was negative. Punch biopsy of a lower back lichenoid lesion demonstrated classic histopathologic criteria for BP. Although a second biopsy demonstrated histopathologic findings consistent with LP, DIF demonstrated linear staining for IgG and C3 at the basement membrane zone (BMZ), classic findings in BP. Indirect immunofluorescence studies were negative. The eruption gradually resolved with topical corticosteroid therapy during the next several months. There have been no recurrences or subsequent formation of bullae. Although bullous LP must be considered in the differential diagnosis, it can be excluded based on histologic and DIF findings. Some postulate that LPP represents a subepidermal acquired bullous dermatosis that arises as a consequence of the development of antibodies to a variety of BMZ constituents, including BP antigen, that have been exposed as a result of the lichenoid process. However, more patients with this rare disease must be studied to fully elucidate its relationship to BP.

Periumbilical Pseudoxantoma Elasticum and Angioid Streaks Associated with Chronic Renal Failure. A. Sapadin,[1] M. Lebwohl,[1] S. A. Teich,[2] D. DiCostanzo,[3] R. Phelps,[1] S. R. Cohen.[3] Departments of Dermatology[1] and Ophthalmology,[2] Mount Sinai School of Medicine and Department of Dermatology,[3] Albert Einstein College of Medicine, New York, NY.

Although periumbilical lesions may be found in the hereditary form of pseudoxanthoma elasticum (PXE), this location as the exclusive site of cutaneous involvement is most commonly seen in the rare entity termed periumbilical perforating pseudoxanthoma elasticum (PPPXE). Patients with PPPXE are generally obese, middle aged, multiparous African-American women and have a history of hypertension. The cutaneous lesions are well demarcated, hyperpigmented, periumbilical plaques with keratotic papules located on the periphery. Extracutaneous manifestations of PXE have been described infrequently. The histopathology reveals that morphologically altered and calcified elastic fibers are found throughout the dermis and are extruded to the skin surface by transepidermal elimination. We describe a patient who shared many features of PPPXE, but exhibited several unusual findings. This 77-year-old mildly obese, multiparous, Hispanic woman had long-standing hypertension, hypertensive nephropathy, and end-stage renal disease requiring hemodialysis. She presented with uremic encephalopathy and was found to have a well-demarcated, hyperpigmented, rectangular-shaped plaque immediately superior to the umbilicus. The plaque was formed by the confluence of several keratotic papules. An isolated papule was observed just inferior to the umbilicus. There were no other cutaneous or mucous membrane lesions. It is noteworthy that bilateral angioid streaks were identified on funduscopic examination. Elevation of serum phosphate was substantial, whereas calcium levels were modestly raised as well. A skin biopsy specimen revealed clumped, fragmented, and calcified elastic fibers in the reticular dermis without transepidermal elimination; a pattern indistinguishable from heritable PXE. Tissue specimens from the normal-appearing skin of the neck and axilla failed to demonstrate evidence of PXE. The present controversy about PPPXE has led some to classify it as a separate entity from the heritable disorder, whereas others speculate that this condition merely represents variable expressivity of PXE in which systemic associations are likely. This ongoing controversy is underscored by the unusual presentation of angioid streaks in our case.

Systemic Lupus Erythematosis and Acquired Complement Deficiency Predisposing to Disseminated Meningococcemia. A. Sapadin,[1] E. J. Bottone,[2] M. Gordon,[1] S. Kurtin,[1] and R. Phelps.[1] Department of Dermatology[1] and Division of Infectious Disease,[2] Mount Sinai School of Medicine, New York, NY.

Disseminated meningococcemia is a serious, often life-threatening infectious disease. The predisposition of individuals with congenital deficiency of the terminal components of complement (C5–C9) to *Neisseria meningitis* (NM) infections is well known. However, it is less well known that patients with acquired complement deficiencies (ACD) caused by complement-depleting underlying illnesses such as systemic lupus erythematosis (SLE) are at risk for meningococcal disease. We report a 20-year-old Hispanic woman with a history of SLE and lupus nephritis who presented with fever, chills, severe headache, photophobia, stiff neck, and abdominal pain. Physical examination revealed an ill-appearing woman with a temperature of 105.1°F and a pulse of 150 bpm. The neck was supple and signs of meningeal irritation were absent. The skin examination was remarkable for multiple petechiae on the extremities. Particularly prominent was a sharply angulated, stellate-appearing purpuric macule on the fourth digit of the left hand. The neurological examination revealed no focal abnormalities. Evidence of arthritis and tenosynovitis was not present. Laboratory tests were significant for hemoglobin (5.2 gm/dL), white blood cell count (4,800/mm^3 with a differential of 89 neutrophils, 10 lymphocytes, and 1 monocyte), blood urea nitrogen (52 mg/dL), creatinine (7.0 mg/dL), urinary protein ($>$300 mg/dL), and erythrocyte sedimentation rate (73 mm/hr). Prothrombin time, partial thromboplastin time, and fibrinogen were within normal limits. Serum C3 (390 mg/dL) and C4 ($<$10 mg/dL) were markedly depressed. The cerebrospinal fluid (CSF) was normal. Testing for NM in the CSF was negative. Skin biopsy and "touch prep" from a purpuric papule were performed at the bedside, the latter revealing Gram-negative intracellular diplococci. Intravenous ceftriaxone therapy was initiated and the patient's clinical course dramatically improved. Histopathologic stains of the skin biopsy showed intravascular fibrin thrombi with neutrophils and suggested the presence of diplococci. Blood cultures grew NM. This case underscores the predisposition of patients with SLE to life-threatening meningococcal disease in the setting of an ACD.

Toxic Epidermal Necrolysis Induced by Anticonvulsant Radiation Therapy Synergism. A. Sapadin, P. Calderon, R. Phelps, M. Gordon, R. Fleischmajer, and M. Lebwohl. Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

Toxic epidermal necrolysis (TEN) is the most severe and dramatic cutaneous drug reaction and has a mortality rate of approximately 30%. Confluent erythema and bullae formation occurs, involving both skin and mucus membranes. Characteristically, there is a positive Nikolsky's sign and the epidermis sloughs off in sheets. Oral anticonvulsants and radiation therapy rarely act synergistically to induce this syndrome. Four such patients have been reported previously in the literature. Our patient was a 62-year-old man with a history of adenocarcinoma of the lung and brain metastases who had completed one cycle of chemotherapy, a full course (18 treatments) of radiation therapy, and had been receiving phenytoin (300 mg daily) for seizure prophylaxis. He was hospitalized for his last cycle of chemotherapy when a severe scalp dermatitis in the field of the cranial irradiation was noted. This spread over the next 36 hours to involve the neck, trunk, proximal extremities, and scrotum. On physical examination a markedly tender erythema with bullae formation and erosions was evident in the above-mentioned distribution. The Nikolsky sign was present and sheets of necrotic epidermis detached with minimal physical trauma. The lips and ears were covered with hermorrhagic and necrotic crusts. Oral erosions and a mild conjunctivitis were present. Frozen-section review demonstrated necrotic keratinocytes at all levels of the epidermis. Routine histologic examination (hematoxylin and eosin) was confirmatory. An antigenic mapping study using antibodies specific for the bullous pemphigoid antigen, laminins 1 and 5, collagen IV, and fibrillin-1 was performed by indirect immunofluorescence. The plane of cleavage in the basement membrane zone was thereby demonstrated to be in the lamina lucida. Discontinuation of the offending drug, meticulous nursing care, topical therapy, and strict vigilance for the earliest signs of sepsis led to reepithelialization within 14 days. TEN resulting from anticonvulsant/radiation therapy synergism begins in the field of irradiation. For this reason, it may be confused with a radiation dermatitis early in its course. However, the severity of erythema, rapidity of evolution, and spread beyond the irradiated field are clues to the true etiology. In view of the fulminant and life-threatening nature of TEN, we believe that discontinuation of these synergistic therapies is indicated at the earliest possible time.

Endocrinology

***Linkage Studies in Autoimmune Thyroid Disease by Microsatellite Marker Analysis: Preliminary Results Using the Candidate Gene Approach.** Y. Tomer, D. Greenberg,[1] G. Barbesino, R. Cobin, and T. F. Davies. Division of Endocrinology and Metabolism, Department of Medicine; [1]Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

The autoimmune thyroid diseases (AITD), Hashimoto's thyroiditis (HT), and Graves' disease (GD) are among the most common human autoimmune disorders and affect up to 5% of the general population. Little is known concerning the susceptibility genes for AITD. However, epidemiological evidence for a genetic susceptibility to AITD is abundant: the diseases cluster in families, they are more common in women, the concordance rate in monozygotic twins is 50 to 70%, and studies have demonstrated an association between AITD and certain human leukocyte antigen (HLA) alleles. However, most of the HLA data are cross-sectional, and the few HLA linkage studies reported have been contradictory. To date there are no linkage studies using markers outside the HLA gene region. We have, therefore, initiated a phased set of studies to determine susceptibility genes for AITD. The preliminary results of the initial phase are reported here. We have studied DNA haplotypes of microsatellite loci in the regions of seven candidate genes: (1) HLA gene region (using microsatellite marker tumor necrosis factor-α (TNF-α); (2) thyrotropin (TSH) receptor (TSHR) gene (markers D14S120, D14S81, D14S78, D14S250, D14S293 flanking the TSH receptor gene on chromosome 14q31); (3) thyroid peroxidase (TPO) gene (marker TPO/G); (4) thyroglobulin (Tg) gene (marker cMYC); (5) IgH gene (marker (IgH@); (6) IDDM4 (marker FGF3); and (7) IDDM5 (markers D6S290 and ESR). One hundred and seven subjects from 19 families were studied, 14 subjects had GD and 32 had HT. Di- and tetra nucleotide repeat polymorphisms were analyzed using radiolabeled polymerase chain reaction followed by electrophoresis through a sequencing gel. Logarithm of odds (LOD) scores were computed using the LIPED program for dominant and recessive modes of inheritance, for recombination fractions of 0.01 to 0.5, and for penetrances of 0.1 to 1.0. The results showed negative LOD scores for the Tg, IgH, IDDM4, and IDDM5 markers. Positive LOD scores were found for certain TSHR markers in a geographically logical sequence (maximal LOD score = 1.043 for marker D14S81). Additionally, low positive LOD scores were found for the TPO marker (maximum LOD score $= 0.420$, $\theta = 0.1$), and for TNF-α (maximum LOD score $= 0.328$, $\theta = 0.1$). Thus, our results demonstrated lack of linkage of AITD to the Tg, IgH, IDDM4, and IDDM5 genes. The preliminary evidence for possible linkage to the TSHR gene region requires further confirmation but may be akin to the linkage to the insulin gene in IDDM.

Lack of Demonstrable Adrenal Suppression in Patients with Acquired Immunodeficiency Syndrome Who Have Taken Megestrol. L. Ahmad, M. Polar, and J. Gladstone. Divisions of Endocrinology and Infectious Diseases, Elmhurst Hospital Center, Mount Sinai School of Medicine, New York, NY.

Objective: To assess the impact of Megestrol on adrenal function in patients with AIDS. It has been suggested previously that the use and discontinuation of this drug may result in chemical evidence of adrenal suppression.

Methods: The setting is a city hospital Infectious Disease Clinic which provides care for approximately 700 infected patients infected with HIV. During a 5-month period, adrenal function testing was performed on 25 patients with AIDS and a CD4 count ≤100, who were found to have orthostatic hypotension. We reviewed the charts of these patients to identify those who had taken Megestrol and tried to determine the impact of the discontinuation of Megestrol on subsequent adrenal function.

Results: Of this group of 25 patients, 18 had not used Megestrol at any time before corticotropin (ACTH) stimulation. Of the remaining seven, two were taking Megestrol at the time of testing. Five of seven patients had taken Megestrol at a dose of 40 or 80 mg orally four times a day from 1 week to 4 months (average 2.75 months), and then discontinued its use. These patients had stopped taking Megestrol between 1 and 4 months before testing (average, 2.55 months). Of the patients who had used Megestrol, then discontinued its use, all five (100%) had a normal cortisol response to ACTH. Only 1 of 25 patients was found had an inadequate cortisol response to ACTH. This patient had never taken Megestrol.

Conclusions: Contrary to a previously published report demonstrating the suppressive effects of Megestrol on the cortisol response to ACTH in patients with AIDS, our review suggests no such effect from the use and abrupt discontinuation of Megestrol in these patients.

Orthostatic Hypotension in Patients with Acquired Immunodeficiency Syndrome. L. Ahmad, M. Policar, M. Shimshi, and J. Masci. Divisions of Endocrinology and Infectious Diseases, Elmhurst Hospital Center, Mount Sinai School of Medicine, New York, NY.

Objective: To assess the frequency and causes of orthostatic hypotension (OH) in patients with AIDS.

Methods: Patients were selected for evaluation from a population of outpatients followed at the Infectious Disease Clinic. All patients seen over a period of 4 weeks, who were HIV+ and had a CD4 count less than 100, were included. Pulse and blood pressure (BP) were measured in supine and upright positions. The patient was said to have orthostatic hypotension (OH) if the following changes were noted when position was changed from supine to upright: 1) systolic BP decrease ≥ 20; 2) diastolic BP decrease ≥ 10, or 3) pulse increase ≥ 20. Serum osmolarity (OSM) was measured in an unselected subset of these patients.

Results: Ninety patients were evaluated for orthostatic changes. Fifty-five of these 90 (61%) met one or more of the criteria for OH. Out of 55 patients with OH, OSM results were available for 34 (62%). Of the 34 patients with OH and OSM determinations, 17 (50%) had OSM values that were considered normal (275–299).

Conclusions: There is a high incidence of OH in patients with AIDS with CD4 less than 100. Based on OSM determinations, factors other than volume depletion may be responsible for OH in half of these patients. Further evaluations are needed to determine the extent to which other factors contribute to OH in AIDS.

Production and Characterization of Monoclonal Antibodies to the Mouse Thyrotropin Receptor Extracellular Domain. Y. Bobovnikova, T. Moran, and P. N. Graves. Department of Medicine and Microbiology, Mount Sinai School of Medicine, New York, NY.

The mouse has served as a critical model for the study of autoimmune thyroid disease mechanisms. We have produced and characterized a series of monoclonal antibodies (mAb) to the mouse thyrotropin receptor extracellular domain (mTSHR-ecd). Affinity purified mTSHR-ecd (amino acids 21–415), expressed in a baculovirus-*Trichoplusia* system, was refolded *in vitro* and used to hyperimmunize female BALB/c mice. Spleens were removed 10 days after a final boost of 25 μg mTSHR-ecd I.P. and I.V. and the cells cloned and screened by enzyme-linked immunosorbent assay (ELISA) with soluble mTSHR-ecd antigen. A panel of 18 high-affinity hybridomas was generated and we have characterized eight of this repertoire. Seven of the hybridomas secreted IgG of subclass 1 isotype and one secreted IgM. Six of the eight antibodies were directed toward cross-reactive epitopes and were not species-specific as evidenced by their recognition of recombinant mTSHR-ecd and human TSHR-ecd, whereas two were highly specific for mTSHR only. mAbs were compared for their reactivity to mTSHR-ecd under folding (ELISA) and nonfolding (Western analysis) conditions. Most mAbs demonstrated similar reactivity to both conformational and linear forms of mTSHR-ecd (arbitrary ratios of 0.3 to 0.7 expressed as OD/densitometry using internal standards). This suggested that most mAbs were generated against linear epitopes. However, one mAb (no. 42), showed significantly higher affinity for folded antigen with an OD/densitometry ratio of 4.1, indicating a preference for a conformational epitope. The identification of a conformationally dependent mAb will add considerable strength to the analysis of murine TSHR maturation within the thyroid cell and the structure-function of resultant receptor isoforms.

Use of Bedside Capillary Blood Glucose Data to Measure the Quality of In-Hospital Diabetes Care. G. Katz, P. L. Linekin, L. G. Newman, C. J. Levy, S. H. Roman. Division of Endocrinology and Metabolism, Mount Sinai School of Medicine, New York, NY.

There are currently no standards of care for the management of diabetes in hospitalized patients. We have previously used the laboratory information system to monitor the quality of in-hospital diabetes care. To improve the specificity and sensitivity of the detection of quality issues in glycemic control of hospitalized patients, we developed the following indicators for severe hyperglycemia (HYPER) and hypoglycemia (HYPO) using bedside capillary blood glucose (CBG) data: 1) CBG > 300 mg% for >24 hours, 2) CBG < 80 mg% at any time. Over a period of 5 months, case managers reviewed 116 cases, 15 with a primary and 101 with a secondary diagnosis of diabetes, using these preset indicators. Cases meeting the indicators were evaluated by a multidisciplinary team in the Division of Endocrinology. Of 116 cases reviewed 49 (42%) met either or both indicators. There were 32 HYPER events and 32 HYPO events, with both HYPO and HYPER indicators met in 15 of 49 cases. Of the 32 HYPER events, 28 (88%) were determined to have associated quality issues, with inappropriate use of insulin or oral agents in 21 (66%) and 7 (22%) cases, respectively. In nine HYPER cases, there was failure to recognize special considerations needed during treatment with high-dose steroids, and in four there was mismanagement of diabetic ketoacidosis (DKA). Of the 32 HYPO events, 30 (94%) had associated quality issues. Inadequate management of HYPO, including lack of prompt recognition, treatment, or follow-up, was found in 94% of cases. Inappropriate use of insulin or oral agents in HYPO was found in 14 (44%) and 13 (41%) cases, respectively. Failure to recognize special considerations for treatment with oral agents in the elderly and renal failure was observed in 3 (9%) cases. Overall, there were determined to be 100 quality issues in the 49 cases, 39 in the HYPER group and 61 in the HYPO group.

We conclude: 1) Our CBG indicators detected potential quality issues in a high rate (42%) of random charts reviewed. 2) Several recurrent process-of-care problems were identified and present potential sites for intervention with continuous quality improvement tools. 3) These data provide evidence for glycemic targets around which to develop standards of care for the management of hospitalized patients with diabetes.

Estrogen Effects on Galanin Immunoreactivity in the Gonadotropin-Releasing Hormone Neurons in Female Mice. G. V. Rajendren and M. J. Gibson. Division of Endocrinology, Mount Sinai School of Medicine, New York, NY.

Galanin is reported to be present in a significant proportion of gonadotropin-releasing hormone (GnRH) neurons in the rat. Expression of galanin immunoreactivity in GnRH neuronal cell bodies reaches its peak in female rats when circulating levels of estrogen are high. The present experiments were undertaken to investigate the role of estrogen in the expression of galanin immunoreactivity in GnRH neurons in female mice. The females were ovariectomized (OVX) and either untreated, or given subcutaneous implants of 5 μg estradiol (E_2) to induce a strong feedback inhibition on lutenizing hormone (LH) secretion. A group of cycling females in proestrus were also included in the studies. Two representative coronal sections were selected from each mouse, one passing through the anterior septum and the other containing the organum vasculosum of lamina terminals (OVLT), for analysis using a confocal laser scanning microscope. The GnRH cell bodies in these sections coexpressing galanin immunoreactivity and those which were in close contact with galanin immunoreactive fibers were counted and compared. In the presence of strong steroid inhibition (OVX-E$_2$) less than 7% of GnRH neurons colocalized galanin, whereas in the other groups, 30 to 37% of the GnRH cells were also immunoreactive for galanin. In contrast, GnRH cells in all groups were closely associated with galanin immunoreactive structures, presumably synapses, with no apparent differences among the groups. GnRH neurons receiving synaptic contacts from galanin immunoreactive fibers were particularly abundant (74–92%) at the level of the OVLT. Thus, galanin immunoreactivity in GnRH neurons during E$_2$ inhibition of LH release was suppressed, in contrast to facilitation of galanin immunoreactivity in GnRH neurons during a period of enhanced LH release (proestrus or OVX). This suggests that galanin may be involved in the steroid modulation of the GnRH system.

This work was supported by grant HD 19077 from the National Institutes of Health.

Gonadotropin-Releasing Hormone Axons Travel with Neuronal, not Glial, Elements When Exiting Preoptic Area Explants. M-C. Rogers, A-J. Silverman,[1] and M. J. Gibson. Division of Endocrinology, and Fishberg Center for Neurobiology, Mount Sinai School of Medicine, and [1]Department of Cell Biology and Anatomy, Columbia University College Physicians and Surgeons, New York, NY.

Gonadotropin-releasing hormone (GnRH) fibers follow defined routes to project to the median eminence (ME) during development. Similarly, GnRH axons grow from intraventricular grafts in hypogonadal mice to innervate the host ME. Using organotypic co-cultures of embryonic (E15) tissue in insert chambers, we showed that GnRH terminals grow from the preoptic area (POA) explant preferentially toward a mediobasal hypothalamus (MBH) explant that includes the ME. These findings suggest the existence of a diffusible factor chemotropic for GnRH axons. The purpose of the present study was to evaluate associations of outgrowing GnRH axons with other elements on the membrane. Postnatal day 1 tissue was used; and, as with E15, GnRH outgrowth was higher in the region facing the MBH ($p < 0.001$). Double labeling for GnRH and glial fibrillary acidic protein, vimentin, or S100 was performed to see if GnRH terminals used a glial substrate to grow on the membrane. Only erratic associations were seen between GnRH and glial processes. Staining for growth-associated protein 43 (GAP-43) labels a general population of neurons elongating their axons. Double staining with GAP-43 and GnRH showed that, in contrast to its effect on GnRH axons, the MBH did not induce a differential outgrowth of those axons labeled with GAP-43. GAP-43 axonal outgrowth extended from all borders of the explants and always grew further from the POA explant than the GnRH fibers. Moreover, GnRH fibers traveled in the company of GAP-43 axons. In some cases, the GnRH axons followed a bundle of GAP-43-reactive fibers and in other instances, GnRH axons appeared to be crossing on a dense network of GAP-43-reactive fibers. Some GnRH axons growing on the membrane were also double-labeled with GAP-43. Whether there is a subpopulation of neurons that provide guidance to GnRH axons remains to be determined.

Supported by grant NS20335, from the National Institutes of Health.

Is Undiagnosed Diabetes a Risk Factor for Stroke in Ethnic Minorities? S. H. Roman, J. Godbold, D. R. Horowitz, J. Weinberger, M. Goldman, and S. Tuhrim. Departments of Medicine, Community Medicine and Neurology, Mount Sinai School of Medicine, New York, NY.

Several surveys have documented that 50% of patients meeting criteria for diabetes in the United States do not have a diagnosis of diabetes. Consequently, these individuals are at unrecognized risk for the associated microvascular and macrovascular complications of diabetes. We assessed the risk of undiagnosed diabetes as a risk factor for stroke in a multiethnic case control study of African Americans, Latinos, and whites in New York City. We compared undiagnosed diabetes defined as a glycohemoglobin level (GHb) >8% in 369 acute stroke patients and 951 community controls with no previous diagnosis of diabetes, who were group-matched by ethnicity. Odds ratios (OR) adjusted for age and sex were calculated: (1) for ethnicity as a risk factor for undiagnosed diabetes among the community controls and (2) for undiagnosed diabetes as a risk factor for stroke in each ethnic group. Among controls, 7 (2%) of 346 whites, 25 (6.8%) of 365 African Americans, and 23 (9.6%) of 240 Latinos had GHb >8% ($p < 0.001$) with mean GHb levels of 9.8%, 9.4%, and 9.4% respectively. The ORs (95% confidence limits) for undiagnosed diabetes in the community were: African Americans versus whites, OR = 3.7 (1.6, 8.7) and Latinos versus whites, OR = 5.3 (2.2, 12.6). Compared with individuals with normal GHb levels, the ORs for stroke in individuals with undiagnosed diabetes were: 2.5 (0.9, 6.8) for whites, 2.4 (1.3, 4.7) for African Americans, and 0.97 (0.37, 2.5) for Latinos.

We conclude: (1) Undiagnosed diabetes was three to five times more prevalent in African Americans and Latinos than in white community controls. (2) Undiagnosed diabetes was associated with an increased risk of stroke in African Americans and whites. These data suggest that undiagnosed diabetes is a public health problem which may help to explain the increased risk of stroke in African Americans relative to whites.

Folding-Dependent Binding of Thyrotropin and Human Thyrotropin Receptor Antibodies to Recombinant Murine Thyrotropin Receptor Extracellular Domain. H. Vlase, N. Matsuoka, P. N. Graves, and T. F. Davies. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

We have previously reported the production, characterization, and purification of the extracellular domain of recombinant mouse thyrotropin receptor (mTSHR-ecd). The mTSHR-ecd (amino acids 22–415) was amplified from CBA/J murine thyroid cDNA, and expressed using the baculovirus-insect cell system. Using a monoclonal antibody (A10) and a rabbit peptide antibody (R397), two major species of mTSHR-ecd (66 kDa glycoslyated and 52 kDa nonglycosylated) were detected by Western blotting. Using Ni^{2+}-NTA-resin chromatography, large amounts of soluble mTSHR-ecd were purified. We have now further characterized the biological activity of this purified mTSHR-ecd preparation. To assess ligand-binding capacity, purified mTSHR-ecd was tested for its ability to compete with ^{125}I-TSH binding to wild-type human thyrotropin receptor (hTSHR) expressed in Chinese hamster ovary (CHO) cells. Purified, folded mTSHR-ecd competed successfully for ^{125}I-TSH binding in a dose-dependent manner, with a binding affinity (50% inhibition) in the region of 10^{-8} M. However, this binding affinity was lower than observed with native soluble TSHR isolated from porcine thyroid plasma membranes (50% inhibition achieved with $\sim 5 \times 10^{-10}$ M), in keeping with the published literature. When mTSHR-ecd was preincubated with the hTSHR expressing CHO cells and then removed before the addition of ^{125}I-TSH, no binding inhibition was achieved, confirming direct binding of the purified mTSHR-ecd preparations to ^{125}I-TSH. Unfolding of the purified mTSHR-ecd accomplished by reduction with dithiothreitol followed by alkylation of the sulfhydryl groups with iodoacetamide, markedly reduced binding inhibition. Thirty percent of the Graves' hTSHR-Ab tested ($n = 15$), recognized folded mTSHR-ecd, but not control antigens. To explore the effect of folding on hTSHR-Ab recognition, MRC research standard B hTSHR-Ab was reacted to both folded and reduced mTSHR-ecd. Although the folded ecd was clearly preferred, the reduced ecd preparation, confirmed to be intact by Western blot, was also recognized, but with a lower affinity. These results demonstrate the successful production of large quantities of biologically active mTSHR-ecd antigen and suggest that, although the ecd of the mTSHR in the absence of the transmembrane region is able to bind TSH, intact holoreceptor may be required for high-affinity ligand binding. The data demonstrate that folding of the mTSHR-ecd is an important determinant in both TSH and hTSHR-Ab binding.

Gastroenterology

Gastrointestinal Complications in Adult Recipients of Cardiac Transplants. U. Mahadevan, A. Kornbluth, A. Gass, J. George, M. Courtney, and S. Lansman. The Mount Sinai School of Medicine, New York, NY.

Objective: A series of adult cardiac transplant recipients were evaluated to determine the prevalence, clinical presentation, and etiology of gastrointestinal (GI) disease.

Methods: A retrospective review of the medical records of 105 consecutive adult cardiac transplants performed at Mount Sinai Medical Center from February 1990 to October 1995 was conducted to determine the number of patients who presented with symptoms requiring consultation from a gastroenterologist. The chief complaint at presentation, time since transplant, and final diagnosis were noted.

Results: Of the 105 cardiac transplant recipients, 40 (38%) developed GI complaints necessitating consultation from a gastroenterologist. The average age was 54.4 years (range, 20–66) with 26 men and 14 women. The average time from transplant was 12.3 months (range, 2 days–58 months). The most frequent complaint was diarrhea, 25% (10/40). Abnormal liver function tests, abdominal pain, and GI bleeding each accounted for 20% (8/40). Reflux was a complaint in 10% (4/40). Nausea, dysphagia, constipation, and cancer surveillance accounted for 5% (2/40). Finally 2.5% (1/40) were referred for jaundice. The most frequent diagnoses were gastroenteritis and drug hepatitis secondary to azathioprine and cyclosporine, accounting for 15% each (6/40). GI polyps or cancers, ulcer disease, and gastritis occurred in 12.5% each (5/40). Complications from cytomegalovirus, colitis, diverticular disease, and gastroparesis were found in 10% of the patients (4/40). Gastroesophageal reflux disease and esophageal candidiasis was diagnosed in 7.5% (3/40). Hepatitis was found in 5% (2/40). Finally, esophagitis, hepatic congestion, small bowel obstruction, perianal abscess, hemorrhoids, cholelithiasis, cholestasis, and osmotic diarrhea from enteral feeds were each found in one patient (2.5%). Six patients required surgery. There were no deaths secondary to GI complications.

Conclusion: GI complications after cardiac transplantation are common, occurring in 38% of the recipients in our series. The most frequent cause for consultation was diarrhea, and the most frequent diagnoses were gastroenteritis and drug hepatitis secondary to immunosuppressive medications. Older patients are at greater risk for GI complications. Although there was no GI-related mortality, the morbidity observed was significant.

Long-term Survival of Unresectable Pancreatic Cancer: State-of-the-Art. H. Snady, H. Bruckner, A. Cooperman, J. Dalton, J. Paradiso, J. Ranson, S. Chong, M. Sung, A. Gattani, S. Brower, L. Kiefer, and J. Mandeli. Mount Sinai School of Medicine, New York, NY. Community Hospital, Dobbs Ferry, NY; Franciscan Health System, Hoboken, NJ.

Pancreatic carcinoma (PCa) accounts for 5% of cancer deaths in the United States. Pancreatectomy (PDR), considered the only chance for long-term survival, can be performed only in about 20% of the patients. To examine the effect of split-course radiation therapy (RT) plus radiopotentiator chemotherapy (FSP) on PCa survival, patients with locally advanced unresectable tumors treated with RT-FSP were compared with those with resectable disease that had PDR without preoperative chemoradiation.

Methods: One hundred thirty-two nonmetastatic PCa patients were seen from January 1989 to June 1996. Histology confirmed adenocarcinoma in 129. To confirm resection status and exclude metastases, laparotomy or CT scan was performed, followed by endoscopic ultrasound (EUS), angiogram, and/or laparoscopy in some. Group 1: 61 patients had locally invasive tumors (T3), diagnosed by laparotomy in 41%. Patients were treated with RT-FSP (split-course RT plus simultaneous 5-fluorouracil, streptozotocin, and cisplatin). Those having prior chemotherapy or RT were excluded. Group 2: 71 patients had successful PDR without preoperative chemoradiation.

Results: Group 1: 24 (34%) had surgery after RT-FSP. The 30-day mortality was 0%. Sixteen (23%) patients were downstaged and PDR was performed. Group 2: 30-day mortality was 4%. In 23 (32%) patients PDR required shaving or resection of vessels (T3 disease). Postoperative chemotherapy and/or RT was given in 48 (68%). Mean survival for Group 1 was 22 months compared with 17 months for Group 2 (earlier stage tumors) ($p < 0.05$). In Group 1, 18 survived, 7 after downstaged tumor resection; 21 survived in Group 2. The only 5-year survivors were from the initially unresectable Group 1.

Conclusions: T3 PCa survival is significantly improved with RT-FSP. Long-term PCa survival is more likely with RT-FSP than initial PDR. Preoperative RT-FSP should precede surgery when tumors are reliably staged as unresectable. Preoperative RT-FSP should be studied for all PCa stages.

General Medicine

†Practicing Medicine under the Influence of the Pharmaceutical Industry. L. Adler, R. Sidlow, and D. Muller. Division of General Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Objective: To assess the extent of interactions between Internal Medicine Housestaff (HS) and Pharmaceutical Representatives (PhR) and to examine the attitudes of HS toward these interactions.

Design: Survey conducted with the use of a self-report questionnaire.

Setting and Participants: Of the 137 HS from the Department of Medicine at the Mount Sinai Medical Center surveyed, 104 completed questionnaires for a response rate of 76%.

Measurement and Results: Seventy percent of those surveyed reported a first exposure to PhR before beginning internship. Among the three hospitals in the HS rotations, interaction with PhR was most common at the Bronx VA Medical Center, followed by Mount Sinai Medical Center and Elmhurst Hospital Center (**Fig. 1**). PhR, Fellows, and Ward Chiefs ranked equally as sources of information about new drugs (**Fig. 2**). The gifts most commonly received were pens (95%), pen lights (65%), handbooks (65%), lunch outside the hospital (59%), textbooks (39%), and dinner outside the hospital (35%). Almost half of the HS (48%) made no distinction between medical and nonmedical gifts, and 39% said that they did not set any limit on the value of a gift that they would accept. Thirty-one percent of the respondents said they felt uncomfortable being approached by PhR, and almost half (49%) felt that PhR did not fulfill a valuable teaching role. Almost half the HS (48%) felt that they were not getting accurate information, but one third said that they never demanded references from the PhR. In addition, one third of HS claimed that their prescribing practices were definitely influenced by these interactions. Only 56% felt that their patients benefited from physician/PhR interactions and 8% felt that their patients actually suffered from these interactions. Although 95% of HS felt that "the company's profit margin" was a PhR primary concern (i.e., as opposed to patient welfare), 72%, 76%, and 83% of HS claimed that there was no conflict of interest in PhR sponsoring speakers, making presentations at conferences, and paying for lunches, respectively. Further analysis of the data revealed that HS who answered "profit margin" but denied the existence of a conflict of interest received overwhelmingly more gifts than those that answered "profit margin" and agreed that there was a conflict of interest (Table 1).

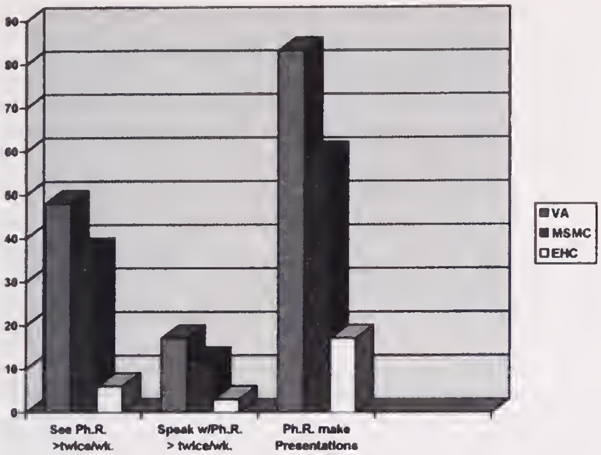


Fig. 1. Percent of HS who interact with PhR. VA, Bronx VA Medical Center; MSMC, Mount Sinai Medical Center; EHC, Elmhurst Hospital Center.

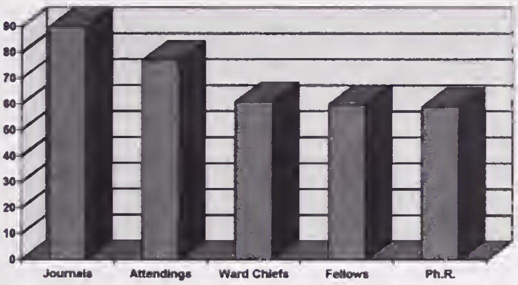


Fig. 2. Sources of information on new drugs. Bars show percent of HS.

TABLE 1
House Staff Receiving Gifts

Gifts Received	"Profit Margin"/ No Conflict $n = 33$ (%)	"Profit Margin"/ Yes Conflict $n = 6$ (%)
Pens	32 (97)	4 (67)
Lights	23 (70)	3 (50)
Handbooks	25 (76)	4 (67)
Textbooks	17 (52)	2 (33)
Drug samples	15 (45)	1 (17)
Lunch	10 (30)	1 (17)
Dinner	18 (55)	1 (17)
Equipment	4 (12)	0 (0)
Gift certificates	2 (6)	0 (0)

Conclusions: Our survey revealed that exposure to PhR begins early and involves a significant amount of promotional items and events. Despite widespread skepticism about the data they receive, HS rely heavily on PhR, are not critical of the information, and many feel that neither they nor their patients benefit from these interactions. Our most provocative finding is the difficulty respondents had in identifying corporate profit margin as a conflict of interest. One possible conclusion is that HS do not know the definition of "conflict of interest." An alternative explanation is that an incentive exists that allows HS to deny the conflict of interest despite the overwhelming evidence. Our data on which HS receive the most gifts supports the latter conclusion.

Early Management of Acute Myocardial Infarction. N. Bishara, M. Schori. Englewood Hospital and Medical Center, Englewood, NJ.

Objective: To compare and contrast the indications for different medical management strategies, revascularization procedures, and predischarge evaluations in management of acute myocardial infarction (MI) between guidelines, results of recent studies, and a community hospital practice.

Design: Retrospective chart review of 45 randomly selected charts of patients admitted to Englewood Hospital Medical Center (EHMC) with acute MI from September 1, 1995 to January 31, 1996. Indications were classified to highly recommended (Class I), recommended with less than enough evidence (Class IIa, IIb), and not recommended, may be harmful (Class III). A Medline search was conducted using keywords: acute MI and thrombolysis, aspirin, β-blockers, heparin, nitroglycerin, calcium channel blockers, antiarrhythmics, warfarin, magnesium, rest 2D-echocardiogram, multiple gated acquisition (MUGA) scan, angiography, percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass graft (CABG).

Results: Compliance was 41% in patients with relative contraindications to B-blockers, 53% in patients with Class III indications for 2-D echocardiography, 12% of patients with Class III indication for 2-D echocardiography, 4% of patients with Class III indication for anigography; 100% of patients with Class I indications for heparin, nitroglycerin, PTCA, and CABG, 83% of patients with Class I indication for aspirin, 100% of patients with Class I indications and 36% of patients with Class IIa indications for angiotensin-converting enzyme (ACE) inhibitors; 100% of patients with Class I indications and 33% of patients with Class IIa indication for chronic anticoagulation. Patients who were not magnesium deficient did not receive magnesium. None of the patients received calcium channel blockers *de novo* on admission or prophylactic lidocaine.

Conclusions: Fifty percent of the study patients were older than 75 years with fewer indications for thrombolysis, anticoagulation, and revascularization procedures. Compliance ranged from overutilization of B-blockers, 2D-echocardiograms, and angiography; to optimal utilization of heparin, nitroglycerin, and MUGA; to underutilization of aspirin, ACE inhibitors, chronic anticoagulation, and magnesium.

Acute Pancreatitis in Human Immunodeficiency Virus-Positive Patients: Characteristics and Predictors of Severity. K. Farrukh, W. Klein, M. S. Shaff. Englewood Hospital and Medical Center Englewood, NJ.

Objective: To perform an analysis of disease characteristics of acute pancreatitis in human immunodeficiency virus (HIV)-seropositive patients as compared with the general population and to evaluate accuracy of predictors of severity.

Study Design and Methods: A retrospective comparative analysis of 15 HIV-positive patients with pancreatitis and 15 non-HIV control patients with pancreatitis under age 50 years hospitalized at Englewood Hospital and Medical Center, Englewood, NJ, from January 1, 1993, to December 31, 1995.

Results: Of 400 patients admitted with acute pancreatitis, 19 had HIV/AIDS (4.75%). Fifteen (3.75%) patients were selected after excluding chronic pancreatitis and readmissions for patients with recurrent pancreatitis. Comparable clinical presentations were observed in patients with HIV and controls except that patients with HIV had more episodes of fever, anorexia, and signs of dehydration. Medications were the most common cause of pancreatitis in the HIV-patient group, followed by possible opportunistic infections. Gallstone pancreatitis was the major cause of pancreatitis in the control group. The Ransom and Glasgow scales were poor predictors of outcome in patients with HIV on admission as compared with assessment after 48 hours (Ransom Scale at 48 hours: sensitivity 28.6%, specificity 62.5%, positive predictive value 40%, negative predictive value 50%). The APACHE II scale proved to be a more useful predictor of disease severity. All three scales predicted severity of illness to almost equal extent in the control group.

Conclusions: Patients with HIV with acute pancreatitis have a presentation that is similar to the general population. However, the causes of pancreatitis in patients with HIV were more varied and included more cases caused by drugs and opportunistic infections. These patients also exhibited signs and symptoms caused by underlying immunosuppression and often had a poor outcome. The APACHE II scoring system can be useful in patients with HIV presenting with pancreatitis for prediction of disease severity at admission and also for daily assessment of hospital course.

Management of Hypercholesterolemia: A Community Hospital-Based Out-Patient Clinic Experience. R. K. Lala, M. P. Schori, and R. P. Soriano. Englewood Hospital and Medical Center, Englewood, NJ.

Objective: To determine the overall compliance of medical residents in the identification, management, and follow-up treatment of patients with hypercholesterolemia in the out-patient clinic of a community hospital.

Study Design: Retrospective review of out-patient clinic charts from April 1993 to March 1996.

Results: Seventy-eight charts with the diagnosis of hypercholesterolemia were reviewed. Fourteen (18%) patients had underlying coronary disease whereas 64 (82%) patients did not. Fifteen (23%) of these patients were followed up by Interns, 27 (42%) patients by PGY-2 residents, and 22 (35%) patients by PGY-3 residents. A favorable trend on the identification and initial follow-up of patients with hypercholesterolemia was observed. No significant difference was seen among the different PGY levels in their management of hypercholesterolemia. An increasing trend toward management of hypercholesterolemia by primary prevention was noted on the performance review since it was emphasized in the summer of 1993. Although the target cholesterol level was achieved in 14 (22%) patients, medical residents still had considerable deficiency in the follow-up of their patients while they were on therapy. Follow-up lipid profiles over time once on treatment, dosage adjustments, and advocation of drug therapy when diet treatment has failed are the areas of concern.

Conclusion: A recognizable trend toward improved identification and initial management of hypercholesterolemia was noted among medical residents at all levels of training. The focus on primary prevention in the summer of 1993 was the major contributing factor to the observed trend. Favorable outcomes of several trials on hypercholesterolemia, stress on primary prevention, and better maintenance of patient records were also contributing factors. However, followthrough of their management, once it was initiated, was deficient and must be emphasized.

Subspecialty Education of the Primary Care Resident: 1996. S. Reichman. Division of General Medicine, Mount Sinai School of Medicine, New York, NY.

The decision of the primary care physician (PCP) to refer a patient to a subspecialist requires formulation of a question concerning need for a procedure, diagnosis, or management. In general internal medicine, 70% to 80% or more of subspecialty problems should be recognized and treated by the PCP. In an era of managed care, referrals should be appropriate and relations with consultants cost-effective. Preliminary studies of consultation requests for pulmonary services by the referring physician at Mount Sinai suggest inadequate thought or learned behavior patterns which may result in inappropriate referrals.

A new educational model is proposed in which a general medical resident (GMR), during block ambulatory or a medical specialty elective rotation, becomes the consultant resident (CR) for problems arising in the *ambulatory* FIRM (group practice). Consultation requests are given to the CR who is supervised by a specialist and/or a fellow. The subspecialist categorizes reasons for consultations, gives feedback to the consultative experience, and creates or reviews established guidelines, when appropriate. The consultant is expected to define those situations in which concomitant care with the PCP and or comprehensive care only by the subspecialist are appropriate as well as those which are inappropriate for subspecialty care referral. In this manner the CR acts not only as a triage agent for the subspecialist, but also as a teacher for the GMR.

Eight educational objectives are identified for the GMR and the CR. Benefits for this model include prompt consultative review of appropriate referrals through resident triage, supervised resident teaching emphasizing common subspecialty medical problems, emphasis on cost-effective patient care studies by reviewing CR consultations, increased communication between primary care and the subspecialty, and development of a base of subspecialty problems encountered during general medical care which are useful for discussion or teaching conferences.

Evaluation of Cross-Cultural Doctor-Patient Relations in a Multidisciplinary Team Setting: 1996. M. Rhee and R. A. David. Division of General Medicine, Mount Sinai School of Medicine, New York, NY.

Objectives: We undertook a study to investigate quality-of-care issues related to language barriers between the patient and physician. Specific issues were to include patient satisfaction, compliance with medication, and health screening examinations.

Methods: An evaluative instrument was developed in the form of a 5-minute survey. Institutional review board approval was obtained. Cases were defined as patients who reported on the survey as using a translator for their visits or as having poor English skills. Patients who reported on the survey as not using a translator and as having good English skills served as controls. Both patient groups were predominantly of Hispanic origin. The survey was administered at Internal Medicine Associates (IMA), a multidisciplinary primary care ambulatory medicine site located in the Primary Care Building at Mount Sinai Medical Center. Data collection was to occur on days patients visited their primary care providers.

Results: Examined were 68 cases and 193 controls. The survey completion rate was 96%. The data are predominantly categorical and a χ^2 analysis was used. A higher percentage of controls reported satisfaction with medical care (93.7 vs 84.4%, $p < 0.05$). Both cases and controls responded that an understanding of side effects corresponds to compliance with medication (86.9% cases, 92.5% controls). A higher percentage of cases claimed that side effects of medication were not explained to them (47.3 vs 16.3%, $p < 0.001$). More controls agreed that their doctors understand how they are feeling, thereby showing a trend, but not reaching statistical significance (84.5 vs 76.2%, $p = 0.13$). Both cases and controls feel they have enough time to communicate with their doctors (89.1% cases, 88.2% controls). Both cases and controls reported that their doctors discuss mammograms or PAP tests (92.3% cases, 88.0% controls). More cases than controls reported having a mammogram within the last 2 years (78.0 vs 60.7%, $p < 0.05$).

Conclusions: The finding that more controls than cases express satisfaction with their medical care leads us to look at the translation process and how we can improve it. Although further investigation is required to pinpoint the causes of this disparity, time spent with the physician was not found to be a factor in our practice. The difference found in the explanation of side effects to medication is a troublesome issue; poor communication regarding side effects needs to be targeted for improvement, because it appears to have an impact on compliance with medication. Interestingly, cases had a higher rate of preventive medical testing. This may in part be caused by the fact that medical testing is often an easier task than is dialogue, and therefore may at times be used as a substitute for verbal communication.

This project was supported by the Patricia S. Levinson Summer Fellowship Program for Innovative Opportunities in Medical Education at Mount Sinai School of Medicine.

Women's Health and Domestic Violence. A. Thomas, C. S. Scheraldi, J. S. Hafi, and M. S. Schori. Englewood Hospital and Medical Center, Englewood, NJ.

Objective: To determine the prevalence of domestic violence in community-based private practice. To validate or refute previously reported clinical characteristics associated with current domestic abuse.

Study Design: Cross-sectional, self-administered, anonymous survey.

Setting: Community-based primary care internal medicine practice in Englewood, NJ.

Subjects: Seventy-seven female patients of varying age, marital, educational, and economic status.

Duration: Thirty days between April 10 and May 10, 1996.

Measurements: Included previously validated questions on physical and sexual abuse, emotional status, demographic characteristics, physical symptoms, use of street drugs, and psychiatric history.

Results: Twelve (15.6%) women were noted to be victims of current domestic violence, eight (10%) had experienced domestic violence at some time in their adult life, and 29 (38%) had experienced violence either as an adult or a child. Currently abused victims were more likely to be African American, Hispanic, or Asian, were more likely to be single, separated, or divorced, and were more likely to be living with a male friend.

Conclusion: One of six women had experienced domestic violence in the previous year, one in ten had experienced violence in her adult life, and one in three had experienced violence either as a child or an adult. Domestic abuse was associated with race, marital status, and h/o living with male friend, substance abuse, psychological and physical symptoms. Physicians should be aware of such high prevalence of domestic violence among their female patients.

Geriatrics

Barriers to Obtaining Consent in Dementia Research: Implications for Surrogate Decision Making: 1994–1996.

S. Baskin, J. Morris, J. Ahronheim, D. Meier, and S. Morrison. Division of Geriatrics, Mount Sinai School of Medicine, New York, NY.

Failure to obtain informed consent from surrogates is an important barrier to research with patients with advanced dementia. Patients with severe dementia were identified through regular rounds for possible participation in a research project on palliative care in end-stage dementias. Next of kin or other appropriate surrogates were approached for informed consent for study participation. One hundred fourteen eligible patients were identified. Consent was obtained in 59 (52%) of these cases. The average age of the patients was 83 years, and 81% were women, 41% were African American, 31% Anglo, 25% Latino, and 3% other ethnic groups. No significant differences were found with regard to age, gender, ethnicity, insurance, and “do not resuscitate” status, feeding tubes, discharge diagnosis, and site of residence between the enrolled and nonenrolled patients. The main reasons for nonenrollment were (1) patients without surrogates (38.2%) which included no next of kin, next of kin unavailable, and next of kin who lacked decisional capacity; (2) the study was not understood despite efforts to clarify and highlight major points of the consent form (20%); (3) other barriers (23.6%) were language difficulties, physician delay/refusal, surrogates feeling overwhelmed or disinterested, and family conflict. Major barriers precluding participation for patients with advanced dementia in clinical research were identified in 49% of eligible subjects. The major barrier to participation in clinical research was the absence of a functional surrogate to participate in medical decision making for patients with dementia. Of eligible subjects with end-stage dementia over a 24-month period 18% were found to have no surrogate for medical decision making. This barrier not only hinders research in dementia, but has important implications for medical decision making for patients with end-stage dementia.

Prevalence of the Use of Digoxin, Beta Blockers and Calcium Channel Blockers in Older Patients with Prior Myocardial Infarction, and Utilization of Calcium Channel Blockers in Older Patients with Hypertension.

D. Fishkind, B. E. C. Paris, and W. S. Aronow. Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY.

In a retrospective study, we analyzed charts of 528 unselected older patients seen from June, 1995 through July 1996 at the Geriatric Practice of the Department of Geriatrics and Adult Development at Mount Sinai Medical Center. The 528 patients included 416 women and 112 men, mean age 81 ± 8 years (range, 58–101). Of 528 patients, 92 (17%) were receiving digoxin, and of these patients 39 (42%) had unclear indications for digoxin documented on their records, as follows: a clinical diagnosis of congestive heart failure with no documentation of abnormal left ventricular ejection fraction (LVEF) in 18 (20%) patients, documented (7 patients) or undocumented (6 patients) paroxysmal atrial fibrillation in 13 (14%) patients, and coronary artery disease (CAD) in 8 (9%) patients. Of 528 patients, 121 (23%) had a prior myocardial infarction (MI), and 175 patients (33%) had CAD. Of the 121 patients with prior MI, 54 (45%) were receiving a calcium channel blocker, 23 (19%) were receiving a beta blocker, and 43 (36%) were receiving an angiotensin-converting enzyme (ACE) inhibitor. Of these 121 patients LVEF was normal in 16 (13%) patients, abnormal in 15 (12%) patients, and not documented in 90 (74%) patients. Of the 173 patients with CAD, 79 (46%) were receiving a calcium channel blocker, 41 (24%) were receiving a beta blocker, and 54 (31%) were receiving an ACE inhibitor. Of these 173 patients, LVEF was normal in 25 (14%) patients, abnormal in 23 (13%) patients, and not documented in 125 (72%) patients. Of 528 patients 420 (80%) were receiving treatment for hypertension. Of the 420 patients with hypertension, 197 (47%) were receiving a calcium channel blocker, 160 (38%) were receiving a ACE inhibitor, 154 (37%) were receiving a diuretic, and 55 (13%) were receiving a beta blocker.

Conclusions: (1) 42% of patients were receiving digoxin who did not have a supraventricular tachyarrhythmia or congestive heart failure with abnormal ejection fraction documented on their record; (2) calcium channel blockers were used more in older patients with prior MI or coronary artery disease than were beta blockers, although beta blockers have been demonstrated to reduce mortality in patients with MI, and calcium channel blockers have not; (3) calcium channel blockers were used more in older patients with hypertension than were ACE inhibitors, diuretics, or beta blockers, although diuretics and beta blockers are recommended as initial drugs in the treatment of older patients with hypertension. In summary, there is a high prevalence of patients who enter the practice having received digoxin for many years, and without a clear understanding of why it was prescribed; physicians seem to be hesitant to discontinue it. Although calcium channel blockers appear to be well tolerated in the very old, at least in the short run, their preferential use in this setting needs to be clearly delineated.

The Effect of Age on Medical Decisions Made for Incompetent Patients.

A. Monias, D. E. Meier, and R. S. Morrison. Division of Geriatrics, Mount Sinai School of Medicine, New York, NY.

The objective of this project is to assess whether age differences between patients and their health care proxies influence the accuracy of proxy decisions in reflecting patient wishes. Two different age cohorts were interviewed: (1) patients from the Mount Sinai Geriatrics Clinic aged 70 years and older; (2) patients from the Mount Sinai AIDS Clinic aged 30 to 50 years. The concepts of resuscitation and artificial nutrition and hydration (ANH) were explained and patients who demonstrated an understanding of both concepts were allowed to continue in the study. Subjects were then asked whether they would choose to have resuscitation and/or ANH for themselves in four hypothetical scenarios: (1) an elderly person in a coma after a car accident; (2) a young person in a coma after a car accident; (3) Alzheimer's dementia; (4) Acquired immunodeficiency syndrome (AIDS) Dementia. The results showed that geriatric patients chose to have resuscitation and ANH at higher percentages than AIDS patients for every scenario except ANH for an elderly person in a coma and resuscitation and ANH in AIDS Dementia. The majority of both old and young patients would choose both resuscitation and ANH in the scenario of a young person in a coma. A majority of both AIDS and geriatric patients would choose neither resuscitation nor ANH in either AIDS or Alzheimer's Dementias. Although this study did not have enough subjects to achieve sufficient statistical power to detect a difference, both older and younger people tend to agree that the younger person is more worthy of life-sustaining therapy in the coma scenario. Another statistically insignificant trend is that older people tend to want more medical intervention than younger people with the exception of the AIDS Dementia scenario. Therefore, patient age may play a role in the decision to accept or refuse life-sustaining therapy; furthermore, generational differences between patient and proxy may contribute to low proxy concordance with patient wishes.

Hematology

†Prenatal Diagnosis of Glanzmann Thrombasthenia using the Polymorphic Markers BRCA1 and THRA1 on Chromosome 17. D. L. French, B. S. Coller, U. Seligsohn, and H. Peretz. Mount Sinai School of Medicine, New York, NY and Chiam Sheba Medical Center, Tel-Aviv University, Israel.

Glanzmann thrombasthenia is an autosomal recessive bleeding disorder caused by mutations in the GPIIb or GPIIIa genes. Both genes map to chromosome 17q21.32, and polymorphisms within this chromosomal region have been identified. Prenatal diagnosis was performed for a family with an affected child (patient CW). CW is a compound heterozygote; his mother's mutation has been identified, but at the time of prenatal diagnosis his father's mutation was unknown. Markers used to determine the probability of the fetus inheriting the father's mutation were:

Locus	Polymorphism	Our Designation
THRA1	$(AC)_n$	0–6
BRCA1	$(CA)_n$	2, 4
GPIIb Bak alloantigen	*Fok*I RFLP[a]	1, 2
D17S579	$(AC)_n$	5
GPIIIa exon IX	*Sma*I RFLP	1, 2
GPIIIa exon VIII	*Taz*I RFLP	1, 2
GPIIIa intron 6	$(CT)_n$	3, 4, 8

[a] RFLP, restriction fragment length polymorphism.

The haplotypes derived from the polymorphisms are shown:

Locus	Father		Mother		Patient CW		Fetal CVS	
THRA1	4	3	6	0	4	0	3	0
BRCA1	2	4	2	4	2	4	4	4
Mutation	m_p	–	–	m_M	m_p	m_M	–	m_M
GPIIIa *Sma*I	2	2	2	1	2	1	2	1
GPIIIa *Taq*I	2	2	1	2	2	2	2	2
GPIIIa $(CT)_n$	4	4	3	8	4	8	4	8

The THRA1 marker was fully informative, identifying the fetus as inheriting the same maternal (0), but a different paternal (3) chromosome than CW (4). The maternal carrier status of the fetus was confirmed by sequence analysis. The BRCA1 and GPIIIa *Sma* I, *Taq* I, and $(CT)_n$ polymorphisms further defined the maternal haplotype, demonstrating that the mutant allele was present in the mother, CW and CVS. From this knowledge, the BRCA1 allele 4 was linked to the maternal mutant allele and the BRCA1 allele 2 was linked to the paternal mutant allele. This led to conclude that the fetus carried the normal paternal allele. From mapping studies, the certainty of diagnosis was >96% based on THRA1 and >98% based on BRCA1. The paternal mutation was subsequently identified and direct sequence analysis of fetal DNA confirmed that the fetus was a carrier. We conclude that chromosome 17 polymorphisms may be useful in prenatal diagnosis and carrier assessment in Glanzmann thrombasthenia.

***Cis*-Platin-Venorelbine and Radiotherapy in Patients with Locoregional Non-Small Cell Lung Cancer, Esophageal, and Laryngeal Squamous Cell Carcinoma: A Preliminary Report.** I. Esseesse, H. Edlis, H. Song, H. Sakurai, O. Dumitrescu, H. Choi, and A. McElhinney. Hematology/Oncology, Radiotherapy, Surgery, Pathology and Radiology Services. Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

Nine male patients, median age 63 (range, 51–78), four with Stage IIIA non-small cell lung cancer (NSCLC), four with esophageal (E) and Laryngeal (L), were treated with a combination of intravenous platin (P), 80–100 mg/m^2 twice every 4 weeks, venorelbine (V), 30 mg/m^2 weekly concomitant radiotherapy (RT), 4000–6300 cGy delivered in 4 to 6 weeks. Four out of nine patients underwent surgical resection of the tumor (two patients with NSCLC, two patients with E). Three patients are awaiting surgery. Two patients, deemed inoperable because of previous head and neck surgery and medical reasons, respectively, received P × 3, V × 13, and RT 6300 cGy. Leukopenia median 2.6 (range, 1.3–4.5), the factor requiring dose modifications and treatment delays, occurred in eight patients, requiring the use of granulocyte-colony stimulating factor in four patients with one of them given antibiotic therapy. No thrombocytopenia was noted; however, a median drop in hemoglobin of 2 gm/dL (range, 2–4) was observed. Two patients developed pain in the tumor site during V injection. One patient had nausea and vomiting Grade 1. In three patients the creatinine reached 1.9 mg%, 1.9 mg%, and 2.3 mg%, respectively. Two patients developed esophagitis; one of them required topical therapy. An overall response rate of 88% was achieved, two patients had a pathological complete remission (pCR), and six had a partial remission; one case was considered stable disease. Of interest is the patient with NSCLC that showed moderate decrease (26%) in tumor size by computed tomography scan, but had no tumor left in the specimen resected (pCR). Severe dysphagia was abated in three patients with E within 3 weeks of treatment, allowing regular diet feeding in two patients. The duration of response ranged from 5+ weeks to 49+ weeks, with two E patients developing a local relapse 33 weeks after chemoradiotherapy (C-RT), and bone metastasis 22 weeks after C-RT-surgery, respectively. All patients are alive at 12+, 14+, 15+, 17+, 18+, 19+, 40+, 42+, and 54+ weeks of follow-up from initial therapy.

Conclusions: P + V + RT is a well-tolerated regimen with acceptable toxicity in patients with E, NSCLC, and head and neck carcinomas. Except for one patient undergoing esophagectomy who required prolonged intubation, the patients tolerated surgery well. More patients and further follow-up will be required to further assess the impact of this regimen on response rate and survival.

The WT1 Gene Induces Epithelial-like Differentiation of a Fibroblast Cell Line. S. Hosono, X. N. Luo, J. D. Licht, and G. F. Atweh. Divisions of Hematology and Molecular Medicine, Mount Sinai School of Medicine, New York, NY.

Wilms' tumor gene (*WT1*) expression is critical for normal kidney development. WT1 expression is low in the developing blastema and rises in the comma and S-shaped bodies, intermediates in the formation of the glomerulus. Expression is then down-regulated, except in the podocytes of the mature glomerulus. In model systems *WT1* can inhibit cellular growth and tumorgenicity and blocks cell entry into the

S-phase. In addition, WT1 may play a role in programmed cell death. This information suggests that WT1 is involved in the initiation and orderly progression of renal differentiation, and the conversion from a mesenchyme to an epithelium, deficiency, or disruption of WT1 function leads to renal anomalies and neoplasia.

We can partially recapitulate the *WT1* differentiation program in a heterologous system (NIH3T3 Fibroblasts), inducing mesenchymal fibroblasts to act like an epithelium, inhibiting cellular growth and inducing cellular adhesion. We found that the *WT1* protein could suppress the tumorigenicity of NIH 3T3 cells transformed with the *ras* oncogene. *WT1* protein could also slow down the growth and alter the morphology of normal NIH 3T3 cells. Both normal and transformed cells expressing *WT1* became flattened in cell culture, had a decreased proliferation rate, and formed fewer colonies in soft agar (in transformed cells). WT1-expressing cells formed smaller and more slowly growing tumors in nude mice with altered histopathology. Parental *ras*-3T3 cells produced tumors consisted of fascicles of elongated cells, while tumors that eventually formed from WT1-expressing, *ras*-transformed cells exhibited epithelial-like pseudoglandular structures. NIH3T3 cells overexpressing *WT1*, when grown in three-dimensional cultures with a combination of basement membrane proteins, also changed their morphology, forming ball-like aggregates similar to those produced by canine kidney epithelial cells (MDCK). In our system with NIH3T3 cells stably transfected with WT1 gene, WT1 expression was correlated with the up-regulation of E-cadherin and types III and IV collagen and down-regulation of vimentin, the latter a characteristic marker of mesenchymal tumors. These data are consistent with genetic data that suggests that WT1 may activate and repress target genes during kidney differentiation.

Bone Marrow Examination in the Evaluation of Unexplained Fever. R. T. Lee and K. L. Kaplan. Department of Medicine, Mount Sinai School of Medicine, New York, NY; Division of Hematology, Elmhurst Hospital Center, NY.

Bone marrow examination is often performed in the evaluation of unexplained fever, especially in patients infected with the human immunodeficiency virus (HIV). The cause of fever may be determined by histologic examination or culture of bone marrow specimens. Our aim was to determine the usefulness of bone marrow examination in the evaluation of unexplained fever.

Thirty-five patients who had undergone bone marrow biopsy ± aspiration from July 1992 through October 1993 for evaluation of fever were identified from records kept by the Division of Hematology at Elmhurst Hospital Center, and their charts were reviewed. Fever of unknown origin (FUO), defined as documented fever greater than 101°F on several occasions without an established etiology after at least 1 week of in-patient evaluation, was present in 24 patients, while 11 failed to meet criteria for FUO. No patients in the FUO group were preterminal. Twenty of the 24 FUO patients (83.3%) were HIV infected, two were HIV negative (8.3%), and HIV status was unknown in two patients (8.3%). The median CD4 lymphocyte count among the HIV-infected patients was 40/uL, with 95% Confidence Interval, (95% CI) of 29–140. The median was identical if the two patients with unknown HIV status were included. The cause of fever was determined by bone marrow biopsy ± aspirate in 5 of the 24 FUO patients (21%), all of whom were HIV positive. Four of the bone marrows were positive for granulomas, later shown to be *Mycobacterium avium* complex (MAC), and one was positive for histoplasmosis. The cause of fever was found in nine patients by other methodologies, and no etiology was identified in ten patients. In the 11 patients who did not meet strict criteria for FUO, results were similar. The median CD4 lymphocyte count was 27.5/μl (95% CI, 14–115). All were HIV positive. The cause of fever was identified by bone marrow in 3 of these 11 (27.3%), with two found to have MAC and one miliary tuberculosis.

Bone marrow biopsy is a useful procedure in the evaluation of fever in patients infected with HIV, whether or not the fever meets strict criteria for FUO. An infectious agent was identified in more than 20% of the biopsies examined. These results confirm previous reports.

Binding of Antibodies to Different Regions of Fibrinogen Indicates That the Fibrinogen Coating Density Affects the Conformation of Immobilized Fibrinogen. K. A. Moskowitz,[1] B. Kudryk,[2] and B. S. Coller.[1] Division of Hematology, Mount Sinai School of Medicine, and the New York Blood Center, New York, NY.

We previously reported that platelets (P) that adhere to and spread on low-density immobilized (immob) fibrinogen (ϕ) (wells coated with 100 μL of 2–5 μg/mL ϕ) are able to bind thromboerythrocytes (erythrocytes coupled with $\sim 10^6$ arginine, glycine, aspartic acid-peptides), whereas P that adhere to and spread on high-density immob ϕ (>30 μg/mL) are unable to bind thromboerythrocytes, apparently because of redistribution of GPIIb/IIIa receptors from the luminal to the abluminal surface. One possible explanation for this finding is that ϕ immob at high density adopts a different conformation than ϕ immob at low density. We have now studied the binding of anti-ϕ monoclonal antibodies (mAbs) that we prepared or were obtained from Dr. Andrei Budzynski, Temple University and Dr. Gary Matsueda, Bristol Myers-Squibb. mAbs were used at 10 μg/mL, and tested against immob ϕ coated at 1 to 100 μg/ml. Three patterns of reactivity were observed: (1) a linear increase in binding to wells coated with 1–5 or 1–10 μg/mL ϕ, followed by a lesser increase or plateau at higher ϕ (mAbs Fd4-4E1, Fd4-7B3, 4-2,4A5, 1D4); (2) minimal reactivity at all ϕ concentrations (mAbs 2C34, GC4-1A12); (3) a biphasic response, with linear increase up to 10 μg/mL ϕ and then a significant decline in binding at higher ϕ (mAbs FPA 19/7, 9C3, 31A9, 311, 1C5-A5/2, 44-3). Biphasic binding was abolished if wells were coated with polyclonal α-ϕ before ϕ adsorption or if ϕ was denatured in 8 M urea. mAbs that demonstrated a biphasic response did not recognize soluble ϕ, suggesting that ϕ immob at 1–10 μg/mL adopts a conformation unlike soluble ϕ, whereas ϕ immob at >30 μg/mL adopts a more solution-like conformation. These differences in ϕ conformation may account, at least in part, for the differences in GPIIb/IIIa redistribution on P adherent to different densities of immob ϕ.

Phase II Study of High-Dose Chemotherapy with Autologous Stem Cell Support in Ovarian Cancer Patients with Persistent or Recurrent Small Volume Disease. E. Scigliano, D. Ripley, S. M. Fruchtman, L. M. Isola, P. R. Dottino, and C. I. Cohen. Department of Medicine and Division of Gynecologic Oncology, Mount Sinai School of Medicine, New York, NY.

Women with advanced-stage ovarian cancer who have residual disease at second-look surgery or recurrent disease have a less than 20% chance of long-term, disease-free survival with standard salvage chemotherapy. Because ovarian cancer shows a dose-response relationship to alkylating agent therapy, we investigated the use of high-dose chemotherapy with stem cell support to improve survival in this high-risk group of patients. Ten patients with Stage IIIc or IV ovarian cancer were entered onto the study. The median age of patients was 50 years. Disease status at time of evaluation consisted of elevated CA-125 only (1), positive cytologic washings only (1) or <2 cm nodular disease (8). All patients underwent bone marrow (BM) harvesting. Because delayed platelet engraftment occurred in the first six patients the protocol was adjusted to include the use of granulocyte-colony stimulating factor (G-CSF)-mobilized peripheral blood progenitor cells (PBPC) in addition to BM. The preparative regimen consisted of Melphalan 60 mg/M^2 and Thiotepa 300 mg/M^2 daily for 3 days followed by stem cell infusion. Supportive care included G-CSF, antibiotics for neutropenic fever, and blood and platelet transfusions as indicated clinically. All patients developed severe mucositis and fever. Hyperbilirubinemia occurred in six patients, with other features of veno-occlusive disease of the liver (increased abdominal girth and weight gain) occurring in four of these patients. Hyperbilirubinemia resolved in all patients, but one, who died of multiorgan failure. Other complications included renal insufficiency in three patients, with one patient requiring hemodialysis, hemorrhagic cystitis (1), pericarditis (1), and pneumonia (3). Neutrophil engraftment (ANC ≥ 1000) occurred at a median of 13 days for four patients who received PBPC and BM (vs 22 days for patients who received BM only). The average time to reach an untransfused platelet count of 20,000 was 22 days for patients receiving PBPC and BM (vs 92 days for patients receiving BM alone). One patient died of multiorgan failure on Day 76 post-transplant. Nine patients are alive from 11 to 30 months post-transplant. Eight of these patients have relapsed a median of 7.6 months (range, 6–23 months) after transplant. One patient is alive with no evidence of disease 12 months post-transplant.

Conclusion: High-dose chemotherapy with stem cell support resulted in a moderate progression-free interval in this high-risk group of patients. However, regimen-related toxicities were severe. Future studies will address the earlier use of high-dose chemotherapy in high-risk patients as well as sequential transplants in an attempt to decrease post-transplant relapse.

Unrelated Donor Bone Marrow Transplantation at Mount Sinai Hospital. E. Scigliano, M. Austin, L. M. Isola, A. Vlachos, J. Lipton, D. Skerrett, O. Rosina, B. Shank, M. DeSancho, G. Ross, A. English, A. Rodriguez, and S. M. Fruchtman. Division of Medicine, Pediatrics, and Radiation Oncology, Mount Sinai School of Medicine, New York, NY.

Bone marrow transplant (BMT) from human leukocyte antigen (HLA)-matched, related donors has been used successfully to treat patients with hematologic malignancies, bone marrow failure syndromes, and immunodeficiency diseases, however less than 30% of patients will have a suitably matched, related donor. Increasingly, volunteer, unrelated donors (VUD) are being used for BMT. Between April 1994 and May 1996, 20 patients underwent BMT at Mount Sinai Hospital (MSH) using a VUD as a source of bone marrow (BM). The median age of patients was 17.5 years (range, 8 months to 62 years). Diagnoses included: chronic myelogenous leukemia (chronic phase-4, accelerated phase-3, blast crisis-1), acute leukemia (7), myelodysplasia (1), familial hemophagocytic lymphohistocytosis (1), aplastic anemia (1), langerhans cell histiocytosis (1), and amegakaryocytic thrombocytopenia (1). Identification of a VUD through the national and international BM donor registries took a median of 5 months (range, 2–15 months). Fifteen patients received BM that was serologically matched at HLA A, B, and DR with five patients receiving marrow with a single, minor serologic HLA mismatch. Seven patients received BM that was molecularly mismatched at one DRB1 allele. Supportive care included intravenous γ-globulin, prophylactic antibiotics including ganciclovir for cytomegalovirus-seropositive patients and growth factor for patients with nonmyeloid malignancies and nonmalignant diseases. All patients received unmanipulated marrow at a median cell dose of 3.35×10^8 nucleated cells/kg. Graft-versus-host disease (GVHD) prophylaxis consisted of Cyclosporine (CSA), methotrexate (MTX), and solumedrol in 17 patients, CSA and MTX in two patients, and CSA and solumedrol in one patient. Engraftment of both neutrophils (≥1000) and platelets (≥20,000) occurred at a median of 25 days. The median length of hospital stay was 41 days. Grade I-II GVHD occurred in five patients and resolved in all. Grade III-IV GVHD occurred in 13 patients. Donor-recipient pairs matched at DRB1 had a lower incidence of severe GVHD (53%) than those mismatched at DRB1 (71%). Eleven patients (55%) died of transplant-related complications including GVHD (3), hemorrhage (2), cardiomyopathy (1), interstitial pneumonia (1), fungal pneumonia (1), venoocclusive disease of the liver (1), viral encephalopathy (1), and multiorgan failure (1). One patient relapsed 157 days post-BMT. Eight patients (40%) are alive with stable donor engraftment a median of 275 days post-BMT (range, 72–619).

Conclusion: BMT using VUD, although associated with high transplant-related morbidity and mortality, is an effective therapy in patients with otherwise incurable hematologic diseases who do not have suitably matched, related donors. Improved molecular methods to identify the HLA antigens involved in GVHD should lead to better matching and a reduction in GVHD which remains a major factor affecting outcome.

Disparate Lympho (5%) Erythroid (69%) Donor to Recipient Chimerism in a β°-Thalassemia Bone Marrow Transplant Recipient with Red Cell Indices Indicative of Apparent Full Engraftment. R. S. Weinberg, A. Vlachos, V. Najfeld, J. Lipton, Y. Galperin, A. Scalise, and S. Fruchtman. Divisions of Hematology and Pediatric Hematology/Oncology, Mount Sinai School of Medicine, New York, NY.

An 8-year-old girl with transfusion-dependent β°-thalassemia (β°-thal) received an human leukocyte antigen (HLA) identical bone marrow transplant (BMT) from her β°-thal trait sister. Before BMT, chromosomal analysis (CA) of phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes (PB) from donor and recipient revealed the patient to have 46, XX with a polymorphic heterochromatin region of chromosome 9 (9qh +), which her sister donor did not have. Thus, donor engraftment could be monitored in nucleated BM and PB cells. Red cell indices for donor and recipient pre- and post-BMT and analysis of donor cell engraftment are below.

Day	Hb	MCV	HbA	HbF	HbA2	% Donor	Cells/ Method
Donor	11.2	59.1	94.2	<2	5.8		
Pre	6.5	68.2	0	7.6	2.4		
+24	8.4	79.1	91.4	2.1	3.7	89	BM/CA
+406	9.7		92.0	4.6	4.6	44	BM/CA
+428	9.8	61.4				34	PB/CA
+730	9.7		90.2	1.3	5.0	5	PB/CA
+1000	10.8	59.8	94.4	0.6	5.2	69	BRU-E/ globin

Within 1 month post-BMT, CA of nucleated BM cells indicated 89% donor engraftment. At approximately 1 year post-BMT, nucleated donor cell engraftment had decreased to 44% and 34% in BM and PB, respectively. At 2 years, PB donor engraftment dropped to a potentially alarming 5%. Recipient red cell indices remained similar to those of the donor, however, there was concern of possible graft rejection. Therefore, erythroid chimerism was examined in erythroid progenitor cell-derived colonies (BUF-E). PB mononuclear cells were cultured with erythropoietin in methylcellulose for 14 days. Individual colonies were incubated for 16 hours with ^{3}H-leucine, and globin synthesis was examined by gel electrophoresis on polyacrylamide gels. Of 41 erythroid colonies, 31 (69%) contained β globin and were threfore of donor origin. Mean β globin synthesis (±SD) in donor-derived colonies was 69 ± 21%. We conclude that donor erythroid cells had a selective advantage over host cells and their engraftment was sustained while the host lymphoid system was reestablished. Thus, in β°-thal, direct study of erythropoiesis, which is of paramount importance in this disorder, must be examined before conclusion regarding chimerism, because chromosomal analysis alone may be misleading.

Ex Vivo Cultured Murine Neonatal Peripheral Blood-Derived Hematopoietic Cells Maintain Their Clonogenic Properties and Engraftment Ability. R. S. Weinberg, L. Isola, P. Rubinstein, Y. Galperin, V. Najfeld, and A. Scaradavou. Mount Sinai School of Medicine, Polly Annenberg Levee Hematology Center, New York, NY; The New York Blood Center, Fred H. Allen Laboratory, New York, NY.

Human umbilical cord blood transplants have been used for the treatment of hematologic malignancies and inherited conditions. We developed a murine model of cord blood transplantation for genetic diseases. Murine near-term fetal and neonatal peripheral blood (FNPB) cells, genetically marked with the human multiple drug resistance transgene, were used for syngeneic transplants into sublethally irradiated adult mice. Donor cells were transplanted either fresh or after *ex vivo* culture. Short-term engraftment was demonstrated by polymerase chain reaction amplification of the transgene in the peripheral blood of all survivors (5 of 7 recipients of fresh, and 3 of 8 recipients of *ex vivo* cultured cells) 2 to 4 months after transplant. We have now characterized murine FNPB progenitor cells with regard to: (1) their ability to be maintained and/or expanded in an *ex vivo* culture system with hematopoietic growth factors, (2) their plating efficiency in methylcellulose before and after *ex vivo* culture, and (3) their long-term engraftment capacity in sublethally irradiated adult recipients. FNPB cells were maintained in liquid cultures with murine stem cell factor (20 ng/mL) for 3 to 8 days. Nucleated cell counts increased 1.4 to 11.6-fold (mean, 3.0; median 2.0; $n = 10$ experiments). The clonogenic properties of the cells were maintained. The types and numbers of colonies observed in methylcellulose after liquid culture, as well as the days of peak growth were similar to those produced by fresh FNPB cells.

FNPB cells	CFU-E	BFU-E	CFU-GM	HPP-CFC
	colonies/10^5 cells (±SD)			
Fresh	78 ± 73	8 ± 8	3 ± 2	2 ± 1
(Days of peak growth)	(2–7)	(6–12)	(10–11)	(19–45)
Ex vivo cultured	105 ± 76	15 ± 21	3 ± 2	1 ± 1
(Days of peak growth)	(6–7)	(7–10)	(10–11)	(21–31)

Evaluation of peripheral blood chimerism by FISH analysis in the recipients revealed 2% to 26% donor cells 4 to 6 months after transplantation. Bone marrow cultures were obtained from two animals: one received fresh cells and was evaluated 8 months after transplant, the other received *ex vivo* cultured cells and was tested 14 months after grafting. The derived hematopoietic colonies tested positive for the transgene, definitely proving long-term engraftment of the donor cells. FNPB transplants can be performed successfully in sublethally irradiated mice. In *ex vivo* cultures FNPB cells undergo modest amplification and maintain their clonogenic characteristics and ability for sustained engraftment. Thus, murine neonatal blood grafts can be used as an animal model for cord blood transplantation for gene therapy studies, in which complete myeloablation is not desirable and partial replacement of defective marrow may be sufficient.

Infectious Diseases

Carcinoma of the Lung in Human Immunodeficiency Virus-Positive Persons. T. W. Cheung, I. Estok, D. Rose, E. Chusid, K. Choi, and H. S. Sacks. Mount Sinai School of Medicine, New York, NY.

Objective: To evaluate the natural history and prognostic factors in human immunodeficiency virus (HIV)-positive persons with carcinoma of the lung.

Methods: We retrospectively reviewed the tumor registry and medical records of the AIDS Clinic of Mount Sinai Medical Center (MSMC) from 1980 to 1995. Over this period, MSMC took care more than 3,000 HIV-infected persons.

Results: A total of 25 patients with HIV and lung cancer were identified: 19 men and 6 women. The median age was 49 (range, 38–66). Risk factors for HIV were intravenous drug abuse (15 patients), heterosexual (7), homosexual (1), and unknown (2). Mean CD4 counts were 186.0 + 188 cells/mm. Two patients had a previous history of pulmonary tuberculosis. Twelve had advanced AIDS. All had a history of smoking and presented with advanced disease. Histology: squamous (14), adenocarcinoma (9), large cell (1), and oat cell (1). Median survival from diagnosis of lung cancer was 6.8 months (Kaplan-Meier); Stage III, 7.3 months; Stage IV, 1.2 months. Lactate dehydrogenase and CD4 counts do not correlate with prognosis. These patients were noted to be younger than other patients with lung cancer.

Conclusions: Patients with HIV infection develop lung cancer at a younger age and present with advanced disease. They undergo a more fulminant course with shortened survivals.

Cervical Dysplasia in Human Immunodeficiency Virus-Infected Women in an Inner City Population. T. W. Cheung, S. Cohen, A. Gurtman, and H. S. Sacks. Mount Sinai School of Medicine, New York, NY.

Objective: To determine the prevalence and risk factors for cervical dysplasia among human immunodeficiency virus (HIV)-seropositive women at an inner city primary care clinic.

Methods: The HIV Clinic of MSMC serves more than 1,500 HIV-infected persons, mostly from the East Harlem area and the South Bronx. A nurse practitioner saw 378 women for routine gynecological examination between January 1, 1993 and December 31, 1995. A Papanicolaou smear was obtained for each patient. Medical records of these patients were reviewed retrospectively.

Results: The prevalence of cervical intraepithelial neoplasia (CIN) was 16.9% ($N = 64$). Their HIV risk factors were heterosexual (41 patients), heterosexual and injection drug use (IDU) (7), IDU (12), transfusion (2), and unknown (2). Their ethnicity was black (35 patients), Hispanic (28), and white (1). Among those with CD4 < 200, 22 were CIN I (Squamous intraepithelial lesion [SIL, low grade), 11 were CIN I-II, and 7 were CIN III (SIL, high grade). Among those with CD4 between 201 and 500, 15 were CIN I, 2 were CIN I-II, and 4 were CIN III. For patients with CD4 > 500, 2 were CIN I and 1 was CIN II. There was a strong association between the degree of immunosuppression and prevalence rate and the degree of cervical dysplasia ($\chi^2 = 33.77$ and 26.37, respectively; $p < 0.001$). However, no association was observed between the degree of cervical dysplasia and risk factors, or age groups.

Conclusions: CIN was common among HIV-infected women in an inner city population. The prevalence rate and the degree of cervical dysplasia increased with degree of immunosuppression.

Thalidomide Heals Human Immunodeficiency Virus-Related Oral Aphthae. J. M. Jacobson, J. Spritzler, J. Greenspan, J. L. Fahey, and J. B. Jackson. Mount Sinai School of Medicine, New York, NY; Harvard School of Public Health, Boston, MA; University of California, San Francisco; University of California, Los Angeles, CA; Johns Hopkins School of Medicine, Baltimore, MD.

National Institute of Allergy and Infectious Diseases-AIDS Clinical Trials Group Protocol 251 was a double-blind, randomized, placebo-controlled study that evaluated the utility of thalidomide as treatment for human immunodeficiency virus (HIV)-associated aphthous ulceration of the mouth. To enter the study, patients needed to have a biopsy confirmed aphthous ulcer of the mouth present for at least 2 weeks and measuring at least 5 mm in diameter. A culture of the ulcer needed to be negative for Herpes simplex. Subjects received either 200 mg of thalidomide or placebo orally once daily for 4 weeks. An interim analysis of the date from the first 45 patients led to a termination of the randomization. The ulcers in 14 (61%) of 23 of patients who received thalidomide healed completely at the end of 4 weeks versus the ulcers in 1 (5%) of 22 patients who received placebo (odds ratio, adjusted for group sequential test, ∞; 99.4% confidence interval, 2.46 to ∞; unadjusted $p = 0.0001$). Partial healing occurred in 21 (91%) of those who received thalidomide versus 4 (18%) of placebo controls (odds ratio, 59.14; 95% confidence interval, 7.5–929.6; unadjusted $p < 0.0001$). Plasma levels of tumor necrosis factor-α (TNFα) and soluble TNFα receptor II increased with thalidomide treatment. Thus, thalidomide is effective in healing HIV-associated oral aphthae. Its effect is unlikely to be mediated through inhibition of TNF.

Epidemiology of Percutaneous Injuries at a 1100-Bed Medical Center: Impact of "Safety" Devices, 1992–1995. M. H. Mendelson, M. Rodriguez, E. Bailey, J. Godbold, R. Solomon, B. R. Meyers, and S. Z. Hirschman. Mount Sinai School of Medicine, New York, NY.

During 46 months (1992–1995) a standard form was used at Mount Sinai School of Medicine (MSMC) to analyze the epidemiology of percutaneous injuries (PIs and impact of safety devices (SDs). Reported were 897 PIs. Devices studied and implemented hospitalwide for varied time periods included: needleless intravenous (i.v.) system (NS), "safety" vacutainer needle (SV), "safety" butterfly (SB), and two "safety" lancets (SLs). Impact on PI rates were:

Device Specific Injuries	Percutaneous Injury Rate (no. PIs/no. mos) Periods (−) SD	Periods (+) SD	p Value
i.v. infusion (IVI)-related injuries	9.7 (107/11)	1.3 (47/35)	<0.0001
Needle i.v. tubing (N/IV)	6.9 (76/11)	0.4 (13/35)	<0.0001
Phlebotomy devices (PDs)*	3.6 (129/36)	2.4 (24/10)*	0.03
Vacutainer needle	0.5 (18/36)	0.1 (1/10)	0.01
Winged steel/butterfly	2.7 (108/40)	1.8 (11/6)	0.09
Needle/syringe for phlebotomy*	0.9 (34/36)	0.1 (1/10)*	0.0002
Lancet	0.6 (26/42)	0.5 (2/4)	0.31

*(+)device includes period with SV + SB and period with SV only. All SDs reduced PIs.

The needleless system (87% reduction in IVI and 94% reduction in N/IV SIs) and safety vacutainer (80%) resulted in the greatest reductions. There was 2^0 reduction of phlebotomy injuries caused by needle/syringes when other "safety" PDs were implemented. Additional study of the "safety" winged steel/butterfly and longer data collection period for "safety" lancets is warranted.

Epidemiology of Sharps Injuries in 1253 General Surgical Intraabdominal Procedures; Implementation of a Blunted Suture Needle. M. H. Mendelson, J. Cunningham, R. Solomon, B. Rynne, I. Mancini, L. Chen, B. R. Meyers, and S. Z. Hirschman. Mount Sinai School of Medicine, New York, NY.

As part of a program to evaluate "safety" devices for sharps injury (SI) prevention, a blunted suture needle (BSN) was piloted and implemented for general surgical intraabdominal procedures (GSAPs) at Mount Sinai Medical Center, an 1100 bed urban teaching hospital. Data were collected during 3 periods: Phase I, baseline (12 months during December 1994 to February 1996; pilot phase (3 months, May to July 1995); and Phase II, implementation (beginning April 1996). A SI form was completed by operating room circulating nurses and confirmed by scrub nurses during Phases I and II. A product evaluation form was completed by surgeons during the pilot phase. During Phase I, 267 (22%) of 1198 cases were co-observed by a study nurse. There were 32 SIs in 1198 cases (Phase I, SI rate, 2.7% for circulating nurse forms; 5.2% for study nurse forms; $p < 0.05$). SIs by sharp type were: 18 suture needle (94% conventional tapered), SN injury rate (18/1198, 1.5%); 6 bovie; 1 scalpel; 2 hollow bore needle; 2 rake retractor; and 3 unspecified. There were 210 cases during Phase II; 14% were observed by a study nurse. There were two injuries (both occurred while suturing) in Phase II; 2 of 210, 0.95% ($p < 0.05$, Phase I SN injury rate compared with Phase II). None of the injuries were co-observed by a study nurse. Activities at time of SI: 14 suturing, 5 holding/retracting tissue, 5 cutting/coagulating, 4 by stray sutures, 1 returning retractor, 1 injecting, 1 preparing for biopsy, and 3 unknown. Eighteen (53%) SIs were incurred during large bowel/colon procedures; the greatest SI rate was in pancreatic (21.4%, $p < 0.05$) and gastroplasty (7.1%, p = NS) procedures. Pilot phase data: BSN resulted in no or slight change in technique (100%); no effect on procedure time and considered positive intervention (91%); no effect on actual procedure, and as easy to use as standard SN (73%). During Phase II BSNs were used in 62% of cases; of those, 74% were PDS BSNs for fascia/closure. In conclusion, GSAPs are associated with a significant SI rate which is underestimated by an operating room nurse-dependent surveillance system. Pancreatic and gastroplasty procedures pose the greatest risk of SIs. BSNs significantly reduced suture injury rates in general surgical procedures.

Prospective Study of Tuberculin Skin Test Conversion in High Risk Health Care Workers at a New York City Medical Center, 1992, 1995. M. H. Mendelson, I. Finkelstein, T. Szulc, R. Solomon, L. Mancini, J. Solomon, B. R. Meyers, J. Adler, and S. Hirschman. Mount Sinai School of Medicine, New York, NY.

As part of a tuberculosis (TB) control program at an 1100-bed New York City hospital, high-risk health care workers (HR HCWs) were followed with every 6-month tuberculin skin test (TST). HCWs who work in nursing units (Us) where patients with pulmonary TB reside and others who perform procedures or have contact with these patients are included as HR HCWs. A dedicated TST nurse plants and reads the TSTs (5TU PPD) at the HCW's work site. From 1992 to July 1995, 3,054 TSTs were planted on HR HCWs who previously tested negative within one year. TST conversion rates were:

Occupation	1992	1993	1994	1995
	%	%	%	%
Nurses	15.29	7.14	2.86	0
Nursing assistant/other	5.30	2.63	4.92	0
Housestaff*	2.93	6.45	0	1.42
Emergency department (ED) Registrars	12.50	4.92	0	5.56
Respiratory therapy	2.04	0	0	

* Note housestaff rotated through other New York City hospitals.

Control measures were implemented: *1992*: expanded TB isolation policy, mandatory education program, dedicated TB Isolation nurse, increase in (−) pressure isolation rooms on nursing Us, ED, AIDS clinic, daily TB laboratory/24 hour AFB turn around, Directly Observed Therapy Program, and modification of air handling in bronchoscopy suite; *1993*: particulate respirator program, sputum induction unit, and modification of air handling AIDS clinic; *1994*: modification of air handling ED waiting area and Narcotics Rehabilitation Center. Engineering and work practice controls have been successful in reducing overall TST conversion rates in HR HCWs. Additional measures including modifications of air handling in general ED areas is currently being implemented.

Surveillance of Vancomycin-Resistant Enterococcus Faecium in a New York City Teaching Hospital. M. H. Mendelson, L. E. Finkelstein, B. R. Meyers, G. Kogan, C. Tejero, J. Troccoli, J. Gaeta, and S. Z. Hirshman. Mount Sinai School of Medicine, New York, NY.

As part of a surveillance program designed to assess the incidence and epidemiology, and control the transmission of vancomycin-resistant enterococcus faecium (VREF) in an 1100-bed New York City hospital, prospective surveillance of VREF isolates was begun in January 1994. Blood, wound, and other sterile sites were included, urine and stool were excluded. Patients were included only at the time of their initial isolate. From January 1994 to December 1995, 254 patients had VREF isolates (112, 1994; 142, 1995); attack rate of 0.36/1000 patient days (0.32, 1994; 0.41, 1995). Units with the greatest number of VREF patients included the Surgical ICU (SICU) (n = 58), followed by the Liver Transplant Unit (OLT U) (26), and the Medical ICU (MICU) (25). Areas with the greatest 1995 attack rates (per 1000 patient days, $p <$ 0.01) were: SICU (6.73), OLTU (1.46), MICU (1.91), respiratory stepdown/cluster unit (1.8). Of note, OLT SICU patients had a 1995 attack rate of 13.8 vs. 3.7 in non-OLT SICU patients ($p < 0.01$). Control measures included special enterococcal precautions for all identified patients (private room, gloves and gowns, dedicated glass thermometer), infection control education (emphasis on VREF in general sessions, dedicated unit based VREF education), quality monitoring for adherence to precautions (unit based), restriction of oral vancomycin, and modification of surgical prophylaxis to eliminate routine vancomycin before liver transplantation. Monthly 1995 attack rates in the SICU ranged from 2.40 to 16.04/1000 patient days, including two peaks of 16.0 in April 1995 and 10.94 in June 1995. Intensive educational efforts from April to August 1995 and quality monitoring (October 1995) were associated with a decline in SICU rates ending with a rate of 6.56 in December 1995.

In conclusion, a surveillance program for VREF at our medical center showed a significant association with SICU, liver transplantation, MICU, and respiratory step-down/cluster units. Heightened control measures in these areas are warranted and should contribute to controlling attack rates in these special populations.

Tuberculosis in Orthotopic Liver Transplant Patients: Increased Toxicity of Recommended Agents: Cure of Disseminated Infection with non-Conventional Regimens. B. R. Meyers, G. A. Papanicolaou, M. H. Mendelson, P. A. Sheiner, S. Emre, and C. Miller. Divisions of Infectious Diseases, Department of Medicine and Mount Sinai School of Medicine, New York, NY.

First-line antituberculous agents are associated with hepatotoxicity in immunocompetent hosts. Increased hepatotoxicity was observed with four-drug standard induction therapy in orthotopic liver transplant (OLT) patients. The objective of the study was to evaluate the efficacy and adverse effects with a novel continuation regimen for treatment of tuberculosis in OLT patients as a longitudinal follow-up study in a University Hospital in New York City.

At Mount Sinai Hospital nine OLT patients developed tuberculosis from 1988 to 1995. Tuberculosis developed at 12 months (mean) post OLT. Eight (88.8%) of nine patients had positive cultures. All *Mycobacterium tuberculosis* isolates were sensitive to isoniazid, rifampin, pyrazinamide, and ethambutol. Seven (78%) of nine patients had disseminated tuberculosis including two patients with meningitis. Standard induction therapy with three or four drugs was given for 2 months (mean). Liver biopsy during induction therapy revealed drug-induced hepatitis in five (88%) of six patients and rejection in six (100%) of six patients. Continuation regimens consisted mainly of ethambutol and ofloxacin; mean length of therapy was 9 months. Patients were followed from 6 months to 7 years post OLT. Seven of nine patients did well with no evidence of tuberculosis or hepatotoxicity after this regimen; two patients died of tuberculosis; one was diagnosed at autopsy, one during induction therapy.

Conclusions: Hepatotoxicity related to the standard induction regimen developed in five (87%) of six patients. Six (88%) of seven patients with disseminated disease were cured with a novel regimen of ofloxacin and ethambutol after induction therapy. Consideration should be given to this novel follow-up therapy in patients without cavitary pulmonary disease who develop hepatotoxicity during induction.

Complications of Surgery in Human Immunodeficiency Virus-Infected Patients. D. N. Rose, L. Estok, M. Collins, and R. Kleban. Divisions of Infectious Disease and General Medicine, Mount Sinai School of Medicine, New York, NJ.

Objectives: To conduct a literature review of complications of surgery in human immunodeficiency virus (HIV)-infected patients and to determine if the postoperative complication rate is higher in HIV-infected than in uninfected patients or in HIV-infected patients with advanced disease stage.

Methods: We searched MEDLINE, AIDSLINE, conference proceedings, and literature citations. We included all studies of five or more HIV-infected patients and noted events within 1 month of surgery.

Results: Seventy-six published reports describe the postoperative courses of 3,217 HIV-infected patients who had 5,268 procedures: 66 descriptive case series, 14 cohort studies, 6 cross-sectional studies, and 1 clinical trial of a dental procedure. Twenty-one reports describe 490 major abdominal operations other than splenectomy: 211 complications (median rate, range of rates: 33%, 0–160%) and 90 deaths occurred (14%, 0–60%). Ten reports describe 500 anorectal operations: 85 complications (8%, 0–77%) and 11 deaths occurred (0%, 0–18%). Ten reports describe events after splenectomy in 166 patients: 58 complications (33%, 0–100%) and two deaths occurred. Eighteen reports documented postoperative complications in HIV-infected and uninfected patients: five reports demonstrated higher complication rates in HIV-infected patients; the remainder did not. The two best constructed studies had conflicting results. Eighteen reports documented postoperative complications in HIV-infected patients at various disease stages: three reports demonstrated higher rates in advanced HIV disease; four reports showed some evidence for higher rates; the remainder did not.

Conclusions: Most reports of complications of surgery in HIV-infected patients are descriptive and therefore conclusions about rates must be interpreted cautiously. Complication rates vary widely for most procedures. Most reports of HIV-infected and uninfected patients found insubstantial differences in rates between groups, although the best constructed study found higher rates in HIV-infected patients. Seven of 18 reports documenting complications in various HIV disease stages found the rates to be higher in more advanced stages; the remainder did not.

Cost Effectiveness of Cytomegalovirus Disease Prevention in Patients with Acquired Immunodeficiency Syndrome: Oral Ganciclovir and Cytomegalovirus Polymerase Chain Reaction Testing. D. N. Rose and H. S. Sacks, Divisions of Infectious Disease and General Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Background: Oral ganciclovir (GCV) has been proven effective in cytomegalovirus (CMV) therapy but two studies of oral GCV in CMV prevention have discordant results: one found it to be 49% effective; the other found no benefit. CMV DNA can be detected by polymerase chain reaction (PCR), suggesting that early disease can be detected and treated before symptoms develop. Both oral GCV and CMV PCR testing are expensive.

Objective and Design: To determine the conditions under which oral GCV is a cost-effective prevention intervention. We used a Markov model to compare no intervention to two prevention strategies: oral GCV for life unless adverse reactions cause termination of therapy; and plasma CMV PCR testing every 3 months with oral GCV prescribed for persons with positive tests.

Patients and Measurements: Hypothetical HIV-infected patients with CD4 $\leq$ 50 cells/μL and positive CMV serologies. Outcome measures included life expectancy (LE), disease-free LE (DFLE), the number of symptomatic CMV disease cases, and the cost to extend life by 1 year.

Results: A cohort of 1,000 patients can expect 134 cases of symptomatic CMV disease during their lifetimes; LE is 11.59 months and DFLE is 10.42 months. If the cohort takes oral GCV, and if oral GCV is 49% effective, they can expect 83 symptomatic CMV cases; LE is 11.75 months and disease-free LE is 11.02 months. The cost per year of disease-free life extended is $293,200 and the cost per year of life extended is $1,762,517. Oral GCV would be cost effective (i.e., costs ≤$100,000 per year life extended) only if it were 49% effective and if the daily dose costs ≤$9. If the cohort has PCR testing, 126 symptomatic CMV cases can be expected; LE is 11.62 months and disease-free LE is 10.51 months. The cost per year of disease-free life extended is $324,344 and the cost to extend total LE is $962,344. PCR testing would be cost effective only if it detects 80% or more of the CMV cases in the presymptomatic state and if the false positive rate is ≤1% and if the test costs ≤$95.

Conclusions: Oral GCV extends LE only minimally at best, although it may have a substantial effect in extending disease free LE. The cost to achieve these gains is great and therefore oral GCV preventive therapy is not cost effective. Periodic PCR testing with oral GCV preventive therapy for those with positive tests has a minimal effect in extending LE or disease-free survival. The cost is also great and therefore PCR testing is not cost effective.

Cost Effectiveness of Viral Load Testing in the Management of Human Immunodeficiency Virus Disease. D. N. Rose. Divisions of General Medicine and Infectious Disease, Mount Sinai School of Medicine, New York, NY.

Background and Purpose. The plasma concentration of human immunodeficiency virus (HIV) RNA has recently been shown to be the best prognostic marker of disease progression. Recent studies suggest that lowering viral levels with antiretroviral drugs leads to a better outcome. As a result viral load testing (VLT) has become a standard of care. Because the test is expensive, an analysis was performed to determine the conditions under which LVT is a cost-effective strategy.

Methods: Hypothetical HIV-infected patients with 2-, 5-, and 10-year life expectancies were studied using a transition-state model. The outcome measure calculated was the cost to extend life by 1 year. Standard clinical management was compared to standard management plus periodic VLT.

Results: Patients with VLT performed three times per year can expect clinical management decisions based on the test results; if the decisions improve annual survival by 0.5%, the cost per year of life extended by VLT is $150,625. Cost-effectiveness ratios increase (worsen) as the frequency of testing increases and decreases (improves) as the frequency decreases. If four tests are performed annually, the cost to extend life by 1 year is $200,833. Cost-effectiveness ratios increase (worsen) as life expectancy increases. If clinical decisions as a result of VLT improve annual survival by 0.5%, it costs $254,200 to extend life by 1 year for patients with a 5-year life expectancy and $449,000 for patients with a 10-year life expectancy. Cost-effectiveness ratios decrease (improve) as annual survival increases as a result of VLT. For patients with a 2-year life expectancy, testing costs $15,129 to extend life by 1 year if annual survival increases by 5%. If tests are performed two to four times annually, costing $600 to $800 per year, and result in annual survival increases of greater than 1% to 3%, VLT costs less than $100,000 per year of life extended.

Conclusions: VLT is a cost-effective clinical monitoring strategy for many HIV-infected patients. If tests are performed two to four times annually and result in increases in annual survival of greater than 1% to 3%, VLT can be considered cost effective and in the range of other accepted disease-monitoring measures.

Utility of the Polymerase Chain Reaction Test for the Rapid Diagnosis of Pulmonary Tuberculosis. D. N. Rose, J. J. Adler, and J. Boyle. Divisions of General Medicine, Infectious Disease, and Pulmonary and Critical Care Medicine, Department of Medicine and Department of Pathology, Mount Sinai School of Medicine, New York, NY.

Background: The *Mycobacterium tuberculosis* polymerase chain reaction (PCR) test is a new method developed to improve the rapid diagnosis of patients with suspected pulmonary tuberculosis. Although the test has high sensitivity and specificity it is far more expensive than conventional tests and may yield results that are discordant with conventional test results.

Objective: To determine the utility of a *M. tuberculosis* PCR test and the optimal diagnostic strategy for hospitalized patients with suspected pulmonary tuberculosis.

Design: We used decision analysis to compare empirical therapy and conventional testing to seven strategies using PCR directly on respiratory specimens of hypothetical patients.

Measurements: Outcome measures included the average time before initiation of effective antituberculosis therapy, the number of patients with delayed therapy, the number of patients without tuberculosis who are treated with antituberculosis therapy, and average hospital lengths of stay and costs.

Results: Addition of the PCR test to conventional testing methods was found to substantially shorten the average time before initiation of effective antituberculosis therapy and to decrease the number of patients with delayed therapy. Some strategies using PCR also substantially decrease the number of patients without tuberculosis who are treated with antituberculosis therapy. Most strategies using PCR shorten the average hospital lengths of stay and costs. The two best strategies are adding PCR testing to conventional tests with treatment of patients with positive PCR tests and substituting the PCR test for the acid-fast-bacilli smear.

Conclusions: Use of *M. tuberculosis* PCR testing directly on respiratory specimens can decrease the number of patients with delayed therapy, length of hospital stay, and costs.

Hepatology

Chronic Hepatitis C in Patients Undergoing Renal Transplant Evaluation. E. Atillasoy, A. Min, R. Knight, D. Wolf, M. Solomon, M. Panico, J. Lockhart, L. Burrows, S. N. Thung, and H. C. Bodenheimer. Departments of Medicine, Pathology, and Surgery, Mount Sinai School of Medicine, New York, NY.

Introduction: Concerns regarding the acceleration of hepatitis C virus (HCV) replication and the development of a cholestatic syndrome in some postrenal transplant (RT) patients has focused attention on the preoperative evaluation. Despite the lack of correlation between aminotransferase activity (ALT) and histologic findings, many centers evaluate only patients with abnormal ALT values pre- or post-RT. We report data from clinical evaluation of HCV-positive enzyme-linked immunosorbent assay RT candidates.

Methods: All patients had recombinant immunoblot assay testing for HCV. Charts were reviewed retrospectively from the period May 1994 to May 1996 for number of risk factors for acquisition of HCV, date of earliest exposure per risk, stigmata of chronic liver disease, liver function tests, prothrombin time (PT), sonography (U/S), and liver biopsy findings.

Results: There were 31 patients (24 M, 7 F) with a mean age of 45.3 years (range, 20–71). Risk factors were not present in two patients. One, two, or three risk factors were present in 6, 15, and 8 patients, respectively, with a mean duration of HCV infection of 10, 16, and 17 years. Immunoblots were positive, indeterminate, and negative in 26, 3, and 2 patients, respectively. Stigmata of chronic liver disease, abnormal ALT, and abnormal PT occurred in 4, 7, and 0 patients, respectively. Ultrasound examination revealed normal liver in 9, parenchymal changes in 6, isolated hepatomegaly in 2, isolated splenomegaly in 2, and portal hypertension with or without cirrhosis in 4 patients. Sonographic abnormalities were seen in 8 of 14 patients with duration of risk factors dating 6 years or less. Liver biopsy findings were consistent with chronic hepatitis C in 12 of 13 patients and showed Stage 0 in 1, Stage I (portal fibrosis) in 3, Stage II (fibroseptum) in 5, and Stage IV (cirrhosis) in 3 patients, respectively. Normal ultrasound was reported in 2 of 3 Stage I cases, 1 of 5 Stage II cases, and 0 of 3 Stage IV cases. Cirrhosis was seen on ultrasound in 2 of 3 patients. Patients with normal ALT values had abnormal ultrasound in 7 of 14 cases. Three patients classified as ≥ Stage II on histology had risk factors of 0 to 8 years in duration.

Conclusions: Despite normal ALT values in 25 of 31 patients, a significant number of patients had clinical, histological, or U/S abnormalities. U/S was insensitive in identifying chronic liver disease. Liver biopsy was useful in defining disease severity which was unrecognized by noninvasive methods.

Higher Than Expected Values of Ceruloplasmin in Fulminant Wilson's Disease. E. Atillasoy, A. Naim, N. Simsek, S. Emre, N. Varma, and H. C. Bodenheimer. Departments of Medicine and Surgery, Divisions of Liver Diseases and Liver Transplantation, Mount Sinai School of Medicine, New York, NY.

Introduction: Early diagnosis of Fulminant Wilson's Disease (FWD) is crucial because mortality is virtually 100% without liver transplantation. Low ceruloplasmin has been reported to be characteristic of FWD, with normal or elevated values being seen in 10 to 15% of FWD. Suggested causes of elevation in ceruloplasmin include: high estrogen state, acute and chronic inflammatory conditions. Causes of low ceruloplasmin includes malnutrition, interference with protein synthesis, excessive urinary or intestinal loss, interference with intestinal absorption of copper, and rarely hepatic dysfunction. Data regarding ceruloplasmin in acute liver failure are scant.

Method: From January 1992 through February 1996, cases of

FWD and non-Wilson's acute hepatic failure (NWHF) were reviewed. Diagnosis of FWD was established based on presence of Kayser-Fleischer rings (1 of 8 patients), urine copper >500 μg/24 hours (5 of 5 patients) < normal < 60 μg >, serum copper >200 μg/dL (4 of 5 patients) < normal < 150 μg >, Coombs negative hemolysis (7 of 8 patients), and/or low (<15 mg/dL) ceruloplasmin levels (2 of 8 patients). Ceruloplasmin was assayed by Roche laboratories turbidmetric system. These data were analyzed using the Mann-Whitney U test.

Results: Liver failure was caused by FWD in 8 cases (mean age, 18.5; range, 4–34 years) and by NWHF in 95 cases (mean age, 32.7; range, 0.5–70 years). Ceruloplasmin in FWD ($n = 7$; mean, 19.8; range, 2–35 years) was not significantly different than NWHF ($n = 39$; mean, 24.1; range, 14–48 years) ($p = 0.13$). In NWHF 10 patients had ceruloplasmin of <20 (one <15). In our FWD group 72% of the patients had normal ceruloplasmin. In our study albumin was the only parameter which had a correlation ($r = 0.94$) with ceruloplasmin for FWD. Other parameters such as prothrombin time, white blood cell count, bilirubin, creatinine, and age did not have a correlation larger than ±0.3 (see Table).

TABLE

Ceruloplasmin Values in Fulminant Hepatic Failure

Disease	n with ceruloplasmin	Ceruloplasmin (mg/dL)
Hepatitis B	4	24.25 ± 4.11
Hepatitis A	1	34
Non A Non B Non C	9	30.83 ± 8.35
Autoimmune	8	23.50 ± 6.14
Drug	7	28.29 ± 10.96
Acetaminophen	6	25.00 ± 6.84
Wilson's	7	19.79 ± 10.51
Other	4	25.50 ± 6.03

Normal ceruloplasmin = 15–50 mg/dL.

Discussion: Unlike other series, ceruloplasmin values were normal in the majority of our FWD cases and in the low or low-normal range in 24% of NWHF cases. The high values of ceruloplasmin in our study could be caused by a variety of factors. The fact that ceruloplasmin and albumin were correlated in FWD could be caused by the ability of the liver to synthesize proteins.

Conclusion: Ceruloplasmin is not a reliable test in the diagnosis of FWD. It is advisable that the clinician look at a constellation of findings including biochemical indices and other clues including urinary copper excretion. Further investigation is needed to understand the factors mediating ceruloplasmin in FWD and fulminant hepatic failure.

Sequence Divergence Between Murine Aspartate Aminotransferase Alleles. M. W. Bradbury and P. D. Berk. Division of Liver Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Mammalian aspartate aminotransferases consist of cytosolic (cAspAT) and mitochondrial (mAspAT) isoforms that play central roles in amino acid metabolism. In a given species, mAspAT and cAspAT are −50% homologous at both the nucleic acid and amino acid levels. Each is highly conserved across many species. Because of both intraspecies homology and interspecies conservation, more than 150 nucleic acid residues are reportedly conserved in all mammalian AspATs sequenced to date.

During differentiation of mouse 3T3-L1 cells to an adipocyte phenotype, mAspAT is up-regulated and expressed *de novo* on the plasma membrane, where it functions as a free fatty acid (FFA) transporter. Up-regulation of mAspAT does not occur during differentiation of other mouse preadipocyte cell lines. In pursuing this observation, we found that the mAspAT in 3T3-L1 cells migrated electrophoretically like the rare *a* allele found in only a few inbred strains, such as FVB. Most strains express the common *b* allele. The difference between the *a* and *b* alleles is unknown. We wished, therefore, to determine the structure of the *a* protein.

As all available 3T3 cDNA libraries were from the parental strain, which we found to be heterogeneous, consisting of both homozygous *aa* and heterzygous *ab* cells, library screening was not successful in isolating an *a* cDNA. Therefore, reverse transcriptase-polymerase chain reaction primers designed to match the flanking sequences of the *b* allele were used to amplify total liver RNA from mice carrying the *a* allele (FVB). Mice carrying the *b* allele (C57BL/6) served as a positive control. A 1.4-kb product was produced from each genotype, and two plasmid clones with the putative *a* allele were sequenced. In the coding region, 11 of 1290 bp differed from the *b* sequence. Seven substitutions were silent; four caused amino acid changes, in each case altering a conserved residue to an amino acid not previously reported at the locus. Two of the latter replaced arginine with less basic amino acid, consistent with the differences in electrophoretic migration between the isozymes. None of the substitutions involved the FFA binding site. Three of the four amino acid changes involved predicted disruption of restriction sites. This was confirmed by mapping of the cDNA clones and restriction fragment length polymorphism analysis of genomic DNA. The identity of the cDNA clones with the *a* allele was further confirmed by RNase protection, using the cloned sequence to probe RNA from animals of both *a* and *b* genotypes.

What is known of allelic variation in proteins is limited mainly to mutations that have a significant effect on phenotype, or highly studied genes such as hemoglobin. The present study suggests that, even for highly conserved proteins, analysis of more variants may demonstrate greater variability than heretofore recognized. The marked divergence between mAspAT alleles was unexpected, suggesting that studies of allelic divergence will be important both in evolutionary studies and understanding genome sequencing data.

Sources of Specificity and Causes of Collateral Damage in Antisense Strategies. A. D. Branch, D. D. Stump, T. Lefkowitz, S. Koyfman, and J. Walewski. Division of Liver Diseases (Dept. of Medicine) and Division of Abdominal Organ Transplantation (Department of Surgery), Mount Sinai School of Medicine, New York, NY.

Development of specific molecular biology-based therapies, such as those using antisense DNA oligonucleotides, antisense RNAs, and ribozymes, will require the ability to inactivate the intended target while not disrupting essential cellular genes. Unfortunately, as we demonstrate, two commonly used techniques, hammerhead ribozyme-mediated cleavage (of hepatitis B virus [HBV] RNA sequences) and RNase H-mediated cleavage (of hepatitis δ RNA sequences), do not have recognition sequences long enough to permit selective inactivation of specific nucleic acids.

In vitro RNA synthesis and polyacrylamide gel electrophoresis were used to compare the extent of hammerhead ribozyme-mediated cleavage of an RNA containing two mismatches to that of an HBV RNA transcript perfectly matched to the ribozyme's recognition sequence. Under a variety of conditions, the mismatched RNA was cleaved to the same extent as the perfectly matched RNA.

Because RNase H plays a major role in the antisense effects caused by DNA oligonucleotides, a transcript containing sequences of the δ agent was hybridized to 15 base-long DNA oligonucleotides and then incubated with RNase H to assess the extent of "fortuitous cleavages" in this model system. Variable results were obtained. In one case, more than 90% of the cleavages took place at sites containing a maximum of six base pairs complementary to the DNA. Less than 10% of the cleavages occurred at the intended (perfectly matched) target site. In cells, the recognition sites for RNase H probably contain no more than 10 base pairs. Any given 10 base-long sequence is likely to be present in a large number of RNAs in each cell. To illustrate the magnitude of the problem this sequence redundancy may cause, we identified the human mRNAs present in GenBank/EMBL with sequences identical with a 10 base-long sequence from a highly conserved region of hepatitis C virus (HCV) RNA. This region has been identified as a potential target for anti-HCV antisense strategies. We found 66 cellular genes that contain this HCV sequence. Many of these genes play important roles in normal cellular metabolism and should be spared inactivation if possible.

One way to minimize collateral damage may be to design interventions aimed at complex nucleic acid structures, rather than simple sequences. Elements of tertiary structure may have the diversity and individuality necessary to allow selective inhibition to be achieved.

Further Characterization of a Putative Fatty Acid Binding Site in the Mitochondrial Isoform of Aspartate Aminotransferase.

F. Guarnieri and P. D. Berk, Departments of Physiology/Biophysics and Medicine, Mount Sinai School of Medicine, New York, NY.

The mitochondrial (mAspAT) and cytosolic (cAspAT) isoforms of aspartate aminotransferase are homologous proteins that catalyze an identical transamination reaction, and also play an important role in import of reducing equivalents into mitochondria via the malate:aspartate shuttle. We have shown that mAspAT is unexpectedly identical with a previously isolated plasma membrane fatty acid-binding protein, and functions as a membrane transporter for long-chain free fatty acids (FFA). In these and other studies mAspAT was shown under appropriate conditions to bind FFA with high affinity (e.g., K_a = 1.2–1.4 × 10^7 M^{-1} for oleate).

To determine how mAspAT binds FFA, the published high-resolution crystal structure of chicken heart mAspAT was read into the molecular modeling program Macromodel, version 4.5. By displaying the tertiary configuration of the α-carbon backbone as a ribbon diagram in which hydrophobic, charged hydrophilic and uncharged hydrophilic residues were color coded, a region densely packed with hydrophobic amino acids, extending from residues 166 to 270, was identified. Further study of this region identified a hydrophobic groove of appropriate dimensions (~500 A^3) to bind long-chain FFA.

To confirm the function of this hydrophobic groove as an FFA binding site, a similar analysis was conducted of the crystal structure of cAspAT which, despite an appreciable amino acid homology, does not bind FFA. This demonstrated that the tertiary, chain-folding configurations of mAspAT and cAspAT are similar, and that cAspAT contains a cleft in the region between residues 166 to 270 virtually identical in configuration with that in mAspAT. Comparison of the amino acid compositions of this region demonstrated an overall homology (~50%) similar to that of the complete proteins. However, this analysis identified 23 residues that were invariant in all known mammalian mAspATs, and different, yet equally invariant, in the corresponding cAspATs. Eight of the differences represent the replacement of hydrophobic amino acids in mAspAT by noncharged, polar [5] or charged [1] amino acids; or replacement of noncharged polar amino acids by charged acidic residues [2] in cAspAT. Thus, despite a similar spatial configuration, there is a much less hydrophobic environment within this region of cAspAT, which is less conducive to binding FFA. Twelve of the 23 substitutions, including seven which alter either hydrophobicity or charge, occur in amino acids at the right and left sides of the entrance to the hydrophobic cleft in mAspAT. Four of these changes (two on each side) are in highly exposed residues. These observations suggest that both spatial configuration and a hydrophobic environment are essential to the FFA-binding properties of mAspAT. This conclusion will be tested by using site-directed mutagenesis to alter individual residues in the binding site region of mAspAT to the cAspAT amino acid, and then determining the effect of the mutation on FFA-binding affinity.

Reliability of Simple Biochemical Indices to Differentiate Fulminant Wilson's Disease from Other Causes of Fulminant Hepatic Failure.

A. Naim and E. Atillasoy. Department of Medicine, Division of Liver Diseases, Mount Sinai School of Medicine, New York, NJ.

Introduction: Early diagnosis of FWD is crucial because mortality is virtually 100% without liver transplantation. Biochemical indices (such as alkaline phosphatase/bilirubin [ALK PH/BILI], aspartate/alanine transferase [AST/ALT and AST/BILI]) have been used in the work up of FWD, although Salie and colleagues questioned their utility in 1992.

Method: From January 1992 through February 1996, cases of FWD and non-Wilson's hepatic failure (NWHF) were reviewed. Diagnosis of FWD was established based on presence of K-F rings, abnormal parameters of copper metabolism, Coombs negative hemolysis, ALK PH/BIL ratio <2, and/or family history. Ratios of the serum ALK PH and AST to total BILI on admission, when available, were obtained. These data were analyzed using the Mann-Whitney *U* test.

Results: Liver failure was caused by FWD in eight cases (mean age, 18.5; range, 4–34 years) and by NWHF in 95 cases (mean age, 32.7; range, 0.5–70 years). ALK PH/BILI was lower in FWD (mean, 4.7; range, 0.1–27.6) than NWHF (mean, 26.4; range 1, 6–323 (p = 0.0004). Similarly, AST/BILI was lower in FWD (mean, 14.1; range, 3.3–35.2) than NWHF (mean, 443.2; range, 1.6–5940.8) (p = 0.0059). The AST/ALT ratio was higher in FWD (mean, 5.8; range, 0.7–18.9) than NWHF (mean, 1.2; range, 0.09–4.1) (p = 0.0007).

	Diagnosis of FWD			
	ALK PHOS/BILI (mg/dL) <2	AST/ALT >4	AST/BILI <25	AST/ALT >4 & AST/BILI <25
Sensitivity	63%	50%	90%	50%
Specificity	92%	96%	72%	100%

Discussion: Although the biochemical indices were significantly different in FWD, these data overlap with NWFD, and hence they can not be used as a definitive measure in making diagnosis. These values can only help in making the diagnosis of Wilson's disease less or more likely.

Conclusion: Even though biochemical indices can help in ruling out FWD, they are not reliable diagnostic tests. It is advisable that the clinician look at the constellation of findings including biochemical indices including other copper parameters and clinical clues.

Transduction of Mammalian Cells by Murine Leukemia Retroviral Vectors: Role of Cellular Glycosylation.

N. Tavoloni, Division of Liver Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Retroviral vectors derived from Moloney murine leukemia virus (MLV) are highly promising tools for delivering genetic material in clinical settings. Because little is known of MLV cell tropism, we have studied the transduction efficiency of recombinant MLV vectors carrying the LacZ (β-galactosidase) gene on various rodent and human cells. Under optimal conditions for *in vitro* cell transduction, primary cultures of adult rat fibroblasts derived from various organs were very poorly transduced by the ecotropic vector (0.02–0.12%) when compared with immortalized cells like the F2408 (42%) and 3Y1 (defined as 100%) lines. Primary cultures of fibroblasts obtained from neonatal (3.7%) or embryonic rat tissues (4.6%) and primary cultures of rat mammary epithelial cells (3–4%) were somewhat more susceptible. Among human cells, nonestablished fibroblasts derived from adult (0.4–1.5%) or embryonic (6–8%) tissues were also poorly transduced by the amphotropic MLV vector, whereas primary cultures of mammary epithelial cells (60–90%) were nearly as susceptible as the immortalized mammary line 184B5 (defined as 100%). Immortalization of rodent fibroblasts by the Polyoma Large T, SV40 Large T, or the E6/E7 genes of human papilloma virus produced a modest or minimal increase in transduction efficiency. Introduction of the oncogenes v-Src, v-Ras, or v-Raf into rodent cells was in most instances associated with a decrease in MLV vector entry and similar results were observed with neoplastic lines of human origin. Variability of transduction efficiency was not related to differences in cellular growth rate and treatment of both ecotropic and amphotropic MLV vectors *in vitro* with deoxyribonucleoside triphosphates and of cells in culture with inhibitors of cellular proteases failed to enhance entry of either vector into permissive cells. However, inhibition of cellular glycosylation with swansonine, 1-deoxymannojirimycin, and, primarily, tunicamycin profoundly affected cellular entry of MLV vectors. Penetration of the ecotropic vector was enhanced by up to 200-fold or more, particularly into cells which were otherwise highly resistant. Transduction by the amphotropic vector was instead inhibited and severely so in the case of primary cultures of human mammary epithelial cells. These findings demonstrate major differences in transduction efficiency of MLV vectors on mammalian cells and indicate that cellular glycosylation plays a critical role in determining cellular tropism of these vectors.

Oncology/Neoplastic Diseases

***Identification of Genes Differentially Expressed in MCF-7 Breast Carcinoma Cells upon Treatment with 17β-Estradiol.** V. Go and B. G.-T. Pogo. Departments of Pathology and Microbiology, Division of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY.

Estrogens are essential for the growth and development of the mammary gland, thus suggesting a role in the evolution of breast cancer and/or the maintenance of the malignant cell. The breast cancer cell line, MCF-7, is a model system for studying the molecular mechanism of the estrogen response. These cells are able to produce tumors with an increased growth rate and metastatic potential in athymic mice upon the co-introduction of 17β-estradiol. To determine the genes involved in increased tumor growth as a result of estrogen induction, total RNA from MCF-7 cells in the presence or absence of 17β-estradiol was extracted and analyzed by differential display. Differentially expressed cDNA fragments were subjected to further screening by slot blot hybridization. Northern analysis was used to reconfirm the differences, and the differentially expressed fragments were cloned and sequenced revealing unique estradiol-induced sequences. The A/3-9 fragment hybridizes to two transcripts, 890 bp and 480 bp. A 6-fold increase in expression levels was seen with increasing estrogen induction. Sequence analysis revealed no homology to sequences present within sequence databases. The C/7-3 fragment detected two transcripts, 1.1 kb and 390 bp, that exhibited a 4-fold increase in expression. The C/7-3 cDNA fragment showed significant, 98.7%, homology to the 3′ end of the thyroid receptor-interacting protein cDNA, TRip 7, recently identified. TRip 7 also has been shown to be 58% homologous to HMG-14 and HMG-17, core nucleosomal binding proteins. A possible down-regulated A/2-3 fragment hybridized with several transcript sizes. Sequence analysis shows that this fragment has 99% homology to the gb/H80092 cDNA fragment present in the dbEST database. Further characterization of these genes and the functions of their products will add insight to the possible mechanisms by which estrogen maintains a malignant cell state.

***Retroviral Transfer of *MDR*1 Hammerhead Ribozyme Efficiently Reverses Multidrug Resistance.** F. S. Wang, Y. Masuda, J. F. Holland, and T. Ohnuma. Division of Neoplastic Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Multidrug resistance (MDR) is now regarded as the major hindrance for successful chemotherapy in patients with malignant disease. One major mechanism of MDR is an overexpression of P-glycoprotein (P-gp), cell membrane glycoprotein which serves as a drug efflux pump. One means to reverse MDR phenotype is to decrease the level of *MDR*1 mRNA and the overexpression of P-gp in tumor cells. To this end, a hammerhead ribozyme directed against the GUC sequence of codon 196 (196 MDR1 Rz) of *MDR*1 mRNA was cloned into a retroviral vector (N2A) containing Pol III promoter. The cloned retroviral vector was transfected into GP+env AM12 cells using calcium phosphate precipitation and the virus titers of viral producer cell lines were determined in NIH3T3 cells. Then the supernatant comprising the packaged retrovirus with the higher titer ($1.5-3.0 \times 10^5$ cfu/mL) was used to infect the multidrug-resistant MOLT-3/TMQ$_{800}$ cells. After selection with G418, a stably transduced MOLT-3/TMQ$_{800}$ cell pool was evaluated for reversal of the MDR phenotype during the period of long-term culture (50 days to date) by the following four experimental parameters: the level of cell sensitivity to vincristine (VCR) (MTT assay); the level of P-gp (Western blot); the expression of *MDR*1 mRNA (Northern blot); and the retrovirus integration into the genomic DNA of the retrovirus-transduced MOLT-3/TMQ$_{800}$ cells (PCR). After the infection, the levels of both P-gp and the *MDR*1 mRNA were reduced by 50% in the retrovirus-infected MOLT-3/TMQ$_{800}$ cells compared with those in the original MOLT-3/TMQ$_{800}$ cells. The cytotoxic effects measured by the MTT assay showed that the original MOLT-3/TMQ$_{800}$ cells were nearly 1,200-fold resistant to VCR, whereas the ribozyme-transduced MOLT-3/TMQ$_{800}$ cell pool became only about 130-fold resistant. Furthermore, the stable integration of ribozyme gene mediated by the retroviral vector was proven by PCR using the genomic DNA sample of transduced MOLT-3/TMQ$_{800}$ cells for up to $\geqslant$50 days. Taken together, our results show that a retrovirus-mediated transfer of the hammerhead ribozyme exerts stable integration of biologically active ribozyme gene and implies that it can be applied clinically as a specific means to restore the chemosensitivity of MDR tumor cells.

***Cyclin A is a Candidate Target Gene for the Promyelocytic Leukemia Zinc Finger Protein.** P. L. Yeyati, R. Shaknovich, J. Li, S. Waxman, and J. D. Licht. Division of Molecular Medicine and Neoplastics Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Acute promyelocytic leukemia (APL) results from the clonal expansion of myeloid cells blocked at the promyelocyte stage of development and accounts for 10% of all acute myeloid leukemias. In a study of therapy-resistant APL patients, a novel translocation, t(11;17) fuses the RARα gene to the promyelocytic leukemia zinc finger (PLZF) gene. Translocation t(11;17) APL is a distinct syndrome because APL patients with t(11;17) do not respond to all *trans*-retinoic acid (ATRA) treatment. This fusion generates two classes of aberrant proteins, PLZF-RARα and RARα-PLZF; both proteins could potentially disrupt the functions of wild-type RARα and/or PLZF, therefore leading to neoplastic transformation.

PLZF is expressed in CD34+ multipotent hematopoietic precursor cells. In the HL60 and NB4 cell lines, PLZF levels decrease as the cells are induced to differentiate with ATRA. It has been demonstrated that PLZF protein is expressed in a distinct spatial and temporal pattern during murine development. Taken together, these data indicate that PLZF plays an important role in mammalian development and probably in the differentiation program of many cell types.

The focus of the studies in our laboratory is to elucidate the wild-type functions of PLZF and to determine the effects of t(11;17) fusion proteins on the function of PLZF. We have identified a PLZF binding site by a PCR-based selection protocol. Strikingly, the promoter of the cyclin A gene contains an element that has a 12/14 base-pair match with the PLZF binding site we have selected. Gel retardation assays revealed that the nine zinc fingers of PLZF bind to this element on the cyclin A promoter and that 500× molar excess of p53 binding site can not compete away the label suggesting that PLZF recognizes this element in a highly specific manner. RARα-PLZF protein contains the transcription activation domain of RARα fused to the DNA binding domain of PLZF. In co-transfection assays, RARα-PLZF activated transcription through the cyclin A promoter. Myeloid cells that stably express PLZF are blocked/delayed at late G1/S stage of the cell cycle and fluorescence-activated cell sorter analysis of these cells revealed that they have elevated levels of cyclin A. In addition, cells acutely infected with a PLZF-expressing retrovirus tend to accumulate in the S-phase of the cell cycle and display elevated levels of cyclin A. In NIH-3T3 fibroblasts, PLZF overexpression also leads to aberrant cyclin A expression and growth retardation. In this cell type we see altered morphology depending whether the infected cells express PLZF. Taken together these data suggest that cyclin A expression is regulated by PLZF protein. Hence we believe that the alteration of the cell cycle may contribute to the pathology of APL.

Use of Arsenic Trioxide (As_2O_3) in the Treatment of Acute Promyelocytic Leukemia (APL). Arsenic Causes Both Apoptosis and Partial Differentiation of NB4 and Fresh APL Cells in Vitro and in Vivo. Z. Chen, G. Q. Chen, X. G. Shi, W. Tang, J. Zhu, S. M. Xiong, J. H. Ni, C. Gazin, S. Waxman, Z. Y. Wang, and S. J. Chen. Shanghai Institute of Hematology, Rui Jin Hospital, Shanghai Second Medical University, Shanghia, China; Hôpital Saint-Louis, Paris, France, Mount Sinai School of Medicine, New York, NY.

Acute promyelocytic leukemia (APL) is characterized by a specific chromosome translocation t(15;17) and expression of PML-RARα chimeric proteins. In our study a clinical remission trial of As_2O_3 at a dose of 10 mg/day for 28 to 54 days induced a clinical remission in 14 (93.3%) of 15 relapsed APL patients. We investigated the effects of As_2O_3 on fresh APL cells and NB4 cells and demonstrated that As_2O_3 had double effects: preferential apoptosis at high concentration (0.5–2 μM) and partial morphologic differentiation at low concentration (0.1–0.5 μM). Degradation of PML-RARα protein was induced at 0.1–2 μM As_2O_3 and probably contributes to these two effects. That PML-RARα could be the target of As_2O_3, as in all *trans*-retinoic acid treatment, was supported by the finding that the only case resistant to As_2O_3 in our clinical trial had lost the PML-RARα transcript at relapse, in contrast to the *de novo* state of the disease. Bcl-2, an inhibitor of apoptosis, was also down-regulated during treatment with As_2O_3. After 3 to 4 weeks of *in vivo* As_2O_3 treatment when leukemic promyelocytes decreased the bone marrow and peripheral blood cells became myelocytic-like and degenerative cells increased. The combination of partial differentiation and apoptosis appear to be the main cellular effects of As_2O_3 in the treatment of APL and appears to be dependent on PML-RARα.

Operative Blood Loss and Transfusions Associated with the Postoperative Course and Survival in Patients Undergoing Pancreatic Resections. K. Cheng, S. T. Brower, and J. D. Cunningham. Division of Surgical Oncology, Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Pancreatic resections are associated with significant operative blood loss (OBL) and perioperative transfusions (TX), which may affect the postoperative course. In addition, TX may have an immunosuppressive effect, which may influence tumor recurrence. A retrospective study was undertaken to evaluate these factors associated with length of stay (LOS), complication rate, and long-term survival. The study group consisted of 74 patients who had undergone either a pancreaticoduodenectomy (n = 55) or total (n = 19) pancreatectomy from 1980 to 1996 at The Mount Sinai Hospital. Operative mortality for this study group was 7.7%. The median OBL was 1000 mL (n = 68), median units of intraoperative packed red blood cells given during TX was 3 (n = 60), and median LOS was 16 days (n = 67). The more common postoperative complications (CX) encountered were delayed gastric emptying (n = 3), pancreatic fistula (n = 4), gastrointestinal hemorrhage (n = 12), sepsis/abscess (n = 8), and wound infection (n = 4), contributing to a 42% morbidity rate. The influence of OBL and TX on LOS, complication rate, and survival were studied by univariate analyses.

Variable	*n*/median LOS (*p* value)	*n*/complication rate (*p* value)	*n*/median survival (*p* value)
≤500 mls blood loss	11/11 days (≤0.059)	12/8.3% (≤0.019)	12/15 months (not significant)
>500 mL	53/16 days	56/45%	46/20 months
≤2000 mL	51/15 days (not significant)	54/33% (not significant)	46/35 months (≤0.023)
>2000 mL	13/17 days	14/57%	12/10 months
TX of ≤2 U	24/12 days (≤0.02)	26/35% (not significant)	24/17 months (not significant)
>2 U	34/17 days	34/38%	29/30 months
TX of ≤4 U	42/15 days (not significant)	44/32% (not significant)	39/35 months (≤0.017)
>4 U	16/16 days	16/50%	14/8 months

OBL and TX adversely influence LOS, and long-term survival, whereas only OBL influences complication rate. With improvements in operative technique to reduce blood loss, the patient may have a postoperative course with fewer CX. Furthermore, reductions in the amount transfused and the use of autologous blood TX may favorably influence mortality after pancreatic resections.

Reversal of Multidrug Resistance by a Liposome-*MDR*1 Ribozyme Complex. Y. Masuda, T. Ohnuma, H. Kobayashi, and J. F. Holland. Division of Neoplastic Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Multidrug resistance (MDR) is a major obstacle in cancer chemotherapy. We have shown that transfection of a b-actin promoter-driven vector containing a ribozyme which cleaves the GUC sequence of codon 196 of *MDR*1 mRNA (196 *MDR*1 Rz) is effective in reversing MDR phenotype. A ribozyme can be transduced two ways, endogenous and exogenous. The former is intracellular transcription of a ribozyme-coding gene and is accomplished with the transfection or infection of ribozyme-producing vector into target cells. The latter is direct introduction of a ribozyme, either by injection into cells, addition to culture medium, or transfection. This time we examined the exogenous delivery of the *MDR*1 ribozyme by liposome-mediated method. The 196 *MDR*1 Rz was constructed from synthetic oligonucleotides containing T7 RNA polymerase promoter by *in vitro* transcription. The ribozyme was mixed with *N*-(1-(2,3-dileoyloxy)propyl)-*N, N, N*-trimethylammonium methyl sulfate (DOTAP) (1:5 w/w) to form a liposomal complex. The complex was used to treat two P-glycoprotein-producing MDR cell lines: MCF-7/R human breast cancer cells resistant to doxorubicin and MOLT-3/TMQ$_{800}$ human ALL cells resistant to trimetrexate (TMQ). The treatment resulted in the reversal of vincristine (VCR) resistance in MCF-7/R cells from 100-fold to 10-fold, whereas no reversal of VCR resistance was accomplished in MOLT-3/TMQ$_{800}$ cells. In MCF-7/R cells the treatment resulted in decreases in *MDR*1 mRNA expression and P-glycoprotein production, whereas no changes in these parameters were seen in MOLT-3/TMQ$_{800}$ cells. Phase-contrast microscopic studies revealed that in MCF-7/R cells treatment with DOTAP led to formation of cytoplasmic vacuoles and treatment with latex beads resulted in the development of shining materials into the cytoplasmic area, indicating that DOTAP and latex beads were incorporated into MCF-7/R cells. In MOLT-3/TMQ$_{800}$ cells hardly any morphological changes occurred after exposure to DOTAP or latex beads. Confocal microscopic imaging showed cytoplasmic fluorescence in MCF-7/R cells after treatment with DOTAP/fluorescein isothyocyanate (FITC)-dextran or FITC-conjugated latex beads. In MOLT-3/TMQ$_{800}$ cells no fluorescence was detected. Treatment with cytochalasin B abolished fluorescence in MCF-7/R cells from either DOTAP/FITC-dextran or FITC-conjugated latex beads. These data show that MCF-7/R cells have high endocytotic activity, whereas MOLT-3/TMQ$_{800}$ cells have little. The endocytotic activity correlated with the success of liposome-mediated transfer of *MDR*1 ribozyme.

3′-Azido-2′,3′-dideoxythymidine Inhibits Cell Growth and Telomerase Activity of Breast Cancer Cells in Vitro. S. Melana, J. F. Holland, and B. G.-T. Pogo. Division of Neoplastic Diseases, Department of Medicine and Department of Microbiology, Mount Sinai School of Medicine, New York, NY.

3′-Azido-2′,3′-dideoxythymidine (AZT) is a thymidine analog that once phosphorylated can be incorporated into eukaryotic DNA. AZT is currently used in the treatment of acquired immunodeficiency, but not as an antitumor agent. Recently, it has been shown that AZT is preferentially incorporated into telomeric DNA causing telomeric shortening. Because of this late property, we have investigated the effects of AZT on a panel of human cancer cell lines which exhibit telomerase activity: MCF-7, T47D, and two cell lines established in our laboratory, a human T4 lymphocytic leukemia cell line (Jurkat cells) and a normal human breast cell line MCF-10F that lacks telomerase activity. The results indicate that AZT inhibits the growth of all cell lines with an IC$_{50}$ ranging from 250 μM to 1.5 mM. The drug also suppresses cell cloning in soft agar and telomerase activity as measured by the "trap" reaction. These findings support the possibility of using AZT as an anticancer agent.

Public Awareness and Attitudes Concerning Genetic Testing for Hereditary Breast Cancer. A. Mogilner, M. Otten, S. Brower, and J. Cunningham. Division of Surgical Oncology, Department of Surgery, Mount Sinai School of Medicine, New York, NY.

The discovery of germline mutations in the BRCA1 and BRCA2 genes has generated public interest in genetic testing for hereditary breast cancer. We conducted a survey of 354 visitors to the Mount Sinai breast clinic and Surgical Oncology private practice to ascertain awareness and attitudes of patients for genetic testing. Classified by age, ethnicity, religion, educational level, income, and by presence of a personal or family history of breast cancer, subjects were questioned about their awareness of the BRCA genes, the availability of genetic testing, and their willingness to be tested. Some of their answers are summarized in Table 1.

The results indicate that awareness about BRCA testing is not consistent for different populations. African Americans, the very young, and the elderly seem to be the least informed. The majority of patients with personal or family history of breast cancer do not desire testing. They should, therefore, be target groups for genetic testing education. Similarly, that individuals with personal or family histories do not express a significantly increased desire to have the test may indicate that they need to be educated about the potential benefits and risks of genetic testing for relatives of breast cancer patients.

TABLE 1

	% Aware of Genes	$p \leq$	% Aware of Test	$p \leq$	% Desire Test	$p \leq$
Age (yrs)						
Under 25	32		40		83	
25–34	29		41		66	
35–44	44	0.01	46	0.01	72	0.01
45–60	59		65		65	
Over 60	48		42		43	
Ethnicity						
African/American	19		30		75	
Caucasian	68	0.01	66	0.01	61	0.68
Hispanic	28		39		68	
Other	42		14		58	
Religion						
Catholic	35		45		69	
Jewish	72	0.01	67	0.01	57	0.43
Protestant	39		45		70	
Other	27		33		69	
Educational level						
Elementary school	6		13		38	
High school	31		41		69	
College	52	0.01	53	0.01	65	0.02
Graduate school	71		65		67	
Other	43		53		75	
Income						
Under $10,000	23		33		61	
$10–29,000	33		42		79	
$30–49,000	61	0.01	63	0.01	58	0.02
$50–69,000	61		59		61	
$70–99,000	78		44		50	
$100 and above	89		71		82	
Personal History						
Yes	66	0.01	66	0.01	52	0.04
No	39		44		69	
Family History						
Yes	59	0.01	47	0.19	68	0.31
No	35		48		66	

The Bystander Effect in Herpes Simplex Virus-1 Thymidine Kinase Gene Therapy Can Be Mediated by the Gap Junction Protein Connexin-43 in a Directional Manner. J. C. Morris,[1] R. Touraine, W. J. Ramsey, J. Higgenbotham, H. Muslow, and R. M. Blaese. [1]Division of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY, and Clinical Gene Therapy Branch, National Center for Human Genome Research, Bethesda, MD.

Transfer of the herpes simplex virus-1 thymidine kinase (HSV-TK) gene into tumor cells confers sensitivity to the toxic effects of the antiviral nucleoside analog ganciclovir. Some tumor cell lines *in vitro* and *in vivo* exhibit the "bystander effect" (BSE), the ability to kill a greater number of cells in the population than the fraction of cells expressing the TK gene. Increasing evidence suggests the BSE is mediated by gap junctional (GJ) intercellular communication by allowing the toxic metabolites of ganciclovir to pass between TK$^+$ and TK$^-$ cells. Neuro-2a murine neuroblastoma cells do not exhibit a BSE. Neuro-2a TK$^+$ and TK$^-$ cells were transfected with pbabeR43 expressing c-DNAs for the rat GJ protein connexin-43 (CxR43) and puromycin resistance as a selectable marker. The BSE was found to correlate with the level of expression of CxR43 by immunofluorescence staining and immunoblotting. When puromycin selection was removed, CxR43 expression declined and the BSE was reduced. An adenovirus vector expressing CxR43 under the control of the cytomegalovirus promoter (Av.C2.CxR43) was found to result in a high level of expression of CxR43 in Neuro-2a cells without selection. The BSE was increased by Av.C2.CxR43 in mixtures of Neuro-2a/TK$^+$ with Neuro-2a/TK$^-$ cells, and in wild-type Neuro-2a cells co-transfected with Av.C2.CxR43 and an adenoviral vector expressing HSV-TK (Av.C2.TK1). A strong BSE was noted if both TK$^+$ and TK$^-$ cells expressed CxR43. A weaker, but significant BSE was seen when only the TK$^+$ or TK$^-$ cells in the mixture expressed CxR43. This directional effect was increased at higher cell densities. MCA 38.2 TK$^+$/TK$^-$ murine colon carcinoma cells which have a strong BSE did not show an enhancement with Av.C2.CxR43.

Conclusions: (1) The BSE in HSV-TK gene therapy appears to be mediated by gap junctions. (2) The BSE cell killing can be conferred by transfection of the connexin-43 (CxR43) gene by an adenoviral vector. (3) Cell lines with initially high BSE do not appear to have enhancement of the BSE with expression of CxR43. (4) In Neuro-2a cells the expression of CxR43 in the TK$^+$ cell line appears to increase the BSE even if the TK$^-$ cells do not express CxR43. An adenoviral vector expressing both HSV-TK and CxR43 is currently under development as a means of enhancing tumor cell killing.

Cytotoxic Effects of the Telomere-Mimic Phosphorothioate Oligonucleotides on Various Human Tumor Cells in Culture. T. Ohnuma, F-L. Li, and J. F. Holland. Division of Neoplastic Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Telomeres are specialized structures at the ends of eukaryotic chromosomes containing both DNA and protein. In humans the DNA component of telomeres consists of a simple tandemly repeated sequence, TTAGGG. Telomeres' function includes chromosomal protection, e.g., protection against end-to-end fusion, normal control of cell proliferation and aiding in gene regulation. In the cells of higher animals, telomere also serves as a "mitotic clock." Thus, consistent with the inability of DNA polymerase to replicate the ends of linear DNA, in normal somatic cells the chromosomes progressively lose telomeric sequence with each cell division and a sufficiently short telomere signals for replicative senescence. In contrast, all immortal cells examined to date show no net loss of telomere length or sequence with cell division, suggesting that maintenance of telomeres is essential for cells to escape from replicative senescence. Telomerase, a ribonucleoprotein that synthesizes telomeric DNA onto chromosomal ends, was shown to be expressed in malignant tumor cells. We tested cytotoxic effects of telomere-mimic oligomers, 5′-d(TTAGGG)$_n$-3′ where $n = 1,2,3$ or 4 (kindly supplied by Lynx Corp., Hayward, CA) in the following nine human tumor cell lines: 2780 ovarian carcinoma, Hep-2 squamous cell carcinoma, VAMT-1 mesothelioma, DND-1A melanoma, MOLT-3 ALL, Jurkat lymphoma, Daudi Burkitt lymphoma, JAR choriocarcinoma, and SK-LMS sarcoma. As controls, two scrambled 24-mers, 5′-d(TGTGAG)$_4$-3′ and 5′-d(GGTTATGAGTTTGAGTGTGTGGAT)-3′, were tested. Monolayer cells were plated in a 24- or 96-well flat-bottomed plate. After overnight growth, 0.1 volume of graded concentrations of drug was added and further incubated for 4 days. At the end of incubation period, viable cells were quantitated using microcytotoxicity (MTT) assay. For cells in suspension culture, cells were plated onto each well, 0.1 volume of drug was added and incubated for 3 days. Afterward, the culture plate was centrifuged, supernatant medium decanted, and the plate subjected to MTT assay. Among the compounds tested, 6-mer was not active in any of the cell lines studied. Increases in the length of oligonucleotides from 12- to 18- and 24-mer resulted in increased cytotoxic activity in sensitive cell lines. Cells in suspension cultures, MOLT-3 and Daudi cells were generally more sensitive than the monolayers (24-mer ID_{90} = 3 μM). Although the cytotoxic effects of authentic 24-mer oligomer were more pronounced than the scrambled oligomers, both of the scrambled 24-mers also showed some degree of cytotoxic activity. Except for modest activity of the 24-mer in two cell lines, DNA-1A and 2780 cells, none of the compounds tested were active against solid tumor cell lines. These data indicate that further study of the telomere-mimic 24-mer is warranted as a possible antileukemia/antilymphoma agents.

Electrospray Tandem Mass Spectrometry for Amino Acid Sequence Determination of Antineoplastic Peptides. J. Roboz, T. Wang, and L. Ma. Division of Neoplastic Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Based on the demonstrated *in vitro* and *in vivo* antineoplastic activity of synthetic tri- and tetrapeptides from which L-*m*-sarcolysin [SL],*m*[di(2-chloroethyl)-amino]-L-phenylalanine is released, the objective has been to correlate peaks with substructure in the electrospray (ESI) spectra of six sarcolysin-containing peptides: L-*m*-SL-L-Arg(NO_2)-L-Norval, L-Ser-L-*p*-FPhe-L-*m*-SL, L-*p*-FPhe-L-*m*-SL-Asn, L-Pro-L-*m*-SL-L-*p*-FPhe, L-*p*-FPhe-L-*m*-SL-L-Met, and L-*p*-FPhe-Gly-L-*m*-SL-L-Norval. Positive and negative, collision-induced decomposition (CID) spectra were obtained from MH^+ and $(M+Cl)^-$ precursors at 50 to 100 V collision energy. Sequence-related ions found: (a) A_1 (N-terminal) and Y_1 (C-terminal) present in all samples, with increased abundance in CID from MH^+; (b) Important Y_2 ions only appear in CID; (c) B_2 ions appear in all CID spectra; (d) B_3 ions appear in tetra peptide. In-chain ions found: A_2Y_2 and B_2Y_2 (tripeptide) and A_3Y_2, etc. (tetrapeptide) ions, when present in CID at high abundance, provided additional sequence confirmation. Other ions useful in identifying amino acids came from three side chains: (a) loss of Cl-containing moieties from SL subunit; (b) loss of side chain from Arg subunit; (c) loss of side chain from Asn subunit. Conclusions: (a) *Positive Ions*: (a) CID yielded high ion abundances and additional structurally important ions; (b) abundant peaks characteristic for sarcolysin were present in all compounds at *m/z* = 259 $[NH_2{}^+ = CH-CH_2-(m)-C_6H_4-N(C_2H_4Cl)_2]$ and, in CID only, *m/z* = 287 $[NH_2-CH(CO)-CH_2-(m)-C_6H_4-N(C_2H_4Cl)_2]$; (c) Identity and sequence of amino acids could be defined unambiguously; (d) CID, in the parent mode, of selected ions may be used for the detection and identification of metabolites. (2) *Negative Ions*: (a) Little structural information from CID; (b) No $(M-H)^-$ ions, but abundant $(M+Cl)^-$ ions which may be used for identification of individual peptides in mixtures used in chemotherapy.

Supported by T. J. Martell Memorial Foundation for Leukemia, Cancer and AIDS Research.

Identification and Expression of MMTV-Like Sequences in Human Breast Cancer. Y. Wang, I. Pelisson, V. Go, J. F. Holland, and B. G.-T. Pogo, Department of Pathology, Division of Neoplastic Diseases, Department of Medicine and Department of Microbiology, Mount Sinai School of Medicine, New York, NY.

We have previously shown that a 660-bp sequence homologous to the *env* gene of MMTV, but not to HER-K, can be detected by polymerase chain reaction (PCR) in 38% of human breast cancers (BC) and in 1.8% of normal breasts. Using long PCR we now report the identification of a 2.8-kb sequence comprising the LTR and *env* genes, which again are homologous to MMTV, but not to the endogenous retrovirus HER-K. To investigate whether the MMTV-like sequence is actively expressed, reverse transcriptase-PCR was performed. It was found that the sequence is expressed in 65% of the BC which were PCR positive and also in a positive BC cell line. These findings support the proposition that a substantial portion of human BC is associated with sequences homologous to MMTV which may in fact be part of a human MTV.

Pulmonary Medicine

Pulmonary Medicine Liver Dysfunction in Sarcoidosis. R. Salazar, G. Kliger, S. Siou, and A. S. Teirstein. Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Purpose: To assess the incidence and clinical impact of abnormal liver chemistries in patients with sarcoidosis.

Methods: The records of 100 patients presenting to the Sarcoidosis Service were reviewed.

Results: Forty-four patients presented with abnormal liver chemistries which were predominately cholestatic in nature. An elevated alkaline phosphatase was the most common abnormality. There was no difference in age, sex, duration of disease, and pulmonary symptomatology in patients with normal and abnormal liver chemistries. Of 22 black patients 64% presented with abnormal liver chemistries compared with 41% of 66 white patients. Gastrointestinal and constitutional symptoms, hepatomegaly, advanced radiographic stages, and restrictive pulmonary dysfunction were found more commonly in patients with abnormal liver chemistries. Of patients with abnormal liver chemistries 89% were treated, usually for progressive pulmonary disease. None received treatment solely for abnormal liver function or hepatosplenomegaly. When treated, significant improvement in liver chemistries was noted in 26 (79%) of 33 treated patients with 13 of these showing complete resolution.

Conclusion/Clinical Implications: Treatment of liver disease in sarcoidosis is effective, but is usually unnecessary unless accompanied by severe symptoms.

Supported by The Catherine and Henry Gaisman Foundation, New York.

Chronic Active Sarcoidosis. S. Siou, G. Kliger, R. Salazar, and A. S. Teirstein. Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Purpose: To characterize the clinical features of chronic active sarcoidosis (CAS).

Methods: One hundred patients with evidence of active sarcoidosis for more than 2 years were classified as CAS and were compared with a simultaneous group of 50 patients whose disease became inactive within the first 2 years. The diagnosis was proven by tissue biopsy or positive Kveim test in all patients.

Results: The CAS group was divided equally among black and white patients. Black patients had more granulomatous skin lesions than whites (32% vs 8%). Both had a preponderance of Stage II chest radiographs, restrictive pulmonary dysfunction, and extrathoracic sarcoidosis. Antimalarial drugs were effective in control of skin lesions and prednisone was the drug of choice for patients with significant pulmonary sarcoidosis. ^{67}Gallium scans were a reliable guide to disease activity. Angiotensin-converting enzyme levels were elevated in only one half of these patients with active disease. In contrast, the majority of the 50 patients with sarcoidosis which abated within 2 years were white, with a higher percentage of Stage I chest radiographs, less pulmonary dysfunction, and rare skin granulomas. Few required treatment.

Conclusion/Clinical Implications: Although most patients with sarcoidosis require no treatment and others achieve lasting improvement with therapy, a small subgroup of patients pursue an active clinical course for many years. CAS is common in black patients with granulomatous skin lesions, in black and white patients with radiographic and physiologic advanced lung disease, and in patients with extrathoracic sarcoidosis.

Supported by The Catherine and Henry Gaisman Foundation, New York.

Desensitization of Airway Responses to Albuterol in Healthy Subjects. E. N. Schachter, M. Shtern, and N. Rienzi. Departments of Medicine and Anesthesiology, Mount Sinai School of Medicine, New York, NY.

We have previously shown that precontracted airway smooth muscle from guinea pig trachea demonstrates desensitization when relaxed by isoproterenol. The current study investigates a similar protocol in healthy human subjects (HHS). Ten healthy human subjects were recruited for a 2-day protocol. On the first day HHS were screened and performed a cumulative dose-response study measuring airway function after inhalation of 3 cc of increasing doses of albuterol (10, 25, 100, 250, 1000 μg). From the individual dose-response curves we selected a dose of albuterol corresponding to approximately a 50 to 75% increase of the maximal measured response. On a second day at least 48 hours later the HHS returned and were challenged with this submaximal albuterol dose. Lung function was measured initially at 5-minute and subsequently at 10-minute intervals for 95 minutes after airway challenge. The response was described using the maximal expiratory flow measured on the partial flow volume curve at a point 60% of vital capacity below total lung capacity [MEF40%(P)]. A typical mean dose-response curve was described for the HHS with EC_{50} of 10 μg and a plateau (E_{max}) of 22% above baseline. Challenge with the submaximal albuterol dose led to an increase over baseline in lung function with a peak value at 20 minutes (19.9 ± 4.1%), which faded rapidly to a plateau of 12.6 ± 3.5% by 40 minutes; this plateau persisted for 95 minutes postchallenge ($F = 2.2$, $p = 0.02$). We suggest that submaximal stimulation of airway β receptors (ABR) in HHS *in vivo* leads to desensitization/resensitization of ABR as it does in tissue and cell models *in vitro*.

Supported in part by National Institute of Occupational Safety and Health RO1-OHO 2593.

Pharmacologic Characterization of Organic Dusts from the Paper Recycling Industry. E. N. Schachter, E. Zuskin, N. Rienzi, S. Maayani, E. Wan, S. Ali, V. Castranova, M. Whitmer, and P. Siegel. Mount Sinai School of Medicine, New York, NY and the National Institute of Occupational Safety and Health, Morgantown, WV.

In a recent study we evaluated workers exposed to paper dust in the paper-recycling industry. Water-soluble extracts from dusts collected from two different processing areas in the recycling plant (PD1 and PD2), were prepared as a 1:10 w/v solution. Dose-related contractions of nonsensitized, guinea pig trachea (GPT) were demonstrated using these extracts. PD1 and PD2 were added to the GPTs in 0.5 log dose increments. Response was measured as a percent of maximal carbachol response. The effects of mediator-modifying drugs, endopeptidase inhibitors, calcium-blocking agents, and capsaicin were tested (see Table 1). Atropine (A) inhibited both PD1 and PD2. Pyrilamine (P), indomethacin (I), LY71883 (L), NDGA (N), and TMB8 (T) had variable effects on PD-induced constriction. Capsaicin (C) depleted irritant nerves of bronchoconstricting mediators, but paradoxically, pretreatment with capsaicin produced, in some cases, mild enhancement of PD contractile responses. We conclude that PD extracts cause dose-related contractions of GPT and that these extracts are inhibited by a wide variety of pharmacologic agents.

TABLE
E_{max} (as a percent of control) for PD1 and 2 after pretreatment with pharmacologic agents

	A	P	I	L	N	T	C
PD1	2*	61*	44*	75	61**	71*	116*
PD2	3*	86	80	70*	87*	60*	84

* $p < 0.01$; ** $p < 0.05$.

Nephrology

Cloning and Functional Reconstitution of a Urate Transporter/Channel. R. G. Abramson, W. Tao, J. Rappaport, M. Richardson, B. A. Knorr, and E. Leal-Pinto. Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Urate has been shown to be transported by both an anion/exchanger and an electrogenic uniporter in renal proximal tubules, but neither transporter has been characterized at the molecular level. Because our prior data suggested that the uniporter shares some immunologic homology with the hepatic enzyme uricase, we have used a polyclonal antibody to affinity purified pig liver uricase as a tool to clone the electrogenic transporter. A unidirectional rat renal cDNA library was screened with the antibody (1.2×10^6 plaques): a single clone (designated UAT) was isolated and sequenced. UAT is 1476 bp with a 966 bp open reading frame. 5′ extension of the sequence by reverse transcriptase-polymerase chain reaction of rat renal poly A^+ RNA by 69 bp indicated that the full-length UAT mRNA was 1545 bp. Northern blot analysis with probes prepared from UAT were confirmatory because an mRNA transcript of ≅1.5 kb was detected in rat renal poly A^+ RNA. Northern analysis of rat multitissue blots indicated that the UAT mRNA was also present, but expressed differentially, in duodenum, liver, lung, heart, spleen, brain, skeletal muscle, and testes. Recombinant protein (with a 6-histidine tag) was made in *Escherichia coli*, affinity purified, and renatured. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis revealed a 36–37 KDa protein which was reactive to the antibody on Western blot. After incorporation in liposomes and fusion with a lipid bilayer made with the same lipids (PS and PE, 1:1) the recombinant protein functioned as a highly selective, potential dependent 10-pS urate channel that was blocked by the antibody in a dose-dependent fashion. Recombinant HIV-1 Tat, prepared identically, showed no channel activity. Of note, the protein encoded by UAT is unique, but has some homology to galectins, galactoside-binding proteins whose functions have not been defined. Because it is widely expressed, we propose that UAT may serve an essential "house-keeping" function to allow urate that is formed during purine metabolism to efflux from cells, thereby obviating intracellular crystallization. Because the kidneys and intestine provide the sole routes for eliminating urate from the body, and secretion is the mechanism that results in urate excretion, it is also proposed that the renal and intestinal UAT channels play an essential role in modulating systemic urate homeostasis. Finally, we suggest that UAT may be the molecular representation of the electrogenic urate transporter that we previously described in rat and rabbit renal proximal tubules.

Human Immunodeficiency Virus-Associated Nephropathy in Transgenic Mice is Due to Renal Transgene Expression. L. A. Bruggeman, C. Meng, S. Quaggin,[1] T. Coffman,[2] and P. E. Klotman. Division of Nephrology, Mount Sinai School of Medicine, New York, NY; [1]Yale University, New Haven CT; [2]Duke University, Durham, NC.

We have previously described an human immunodeficiency virus-1 (HIV-1) transgenic mouse line that manifests progressive glomerulosclerosis and microcystic tubulointerstitial lesions that resemble HIV-associated nephropathy (HIVAN) in man. One of the major issues in both HIVAN and the murine model is whether the kidney disease is caused by a "bystander" phenomenon in which pathogenesis is mediated by systemically dysregulated cytokines, chemokines, or growth factors. Alternatively, expression of the transgene in kidney or the direct effects of viral proteins may mediate the renal disease. To address this issue, Day F12 fetal kidneys were removed from transgenic and nontransgenic littermates and grown in cell culture. Kidneys were then treated with UV light (254 nm) at a dose previously shown to activate the HIV-1 promoter *in vitro* to up-regulate renal transgene expression terminal deoxynucleotide transferase mediated dUTP-biotin nick-end labeling (TUNEL) assay and electron microscopic analysis of fetal explants indicated significant increases in apoptosis in only transgenic kidneys, suggesting that expression of the transgene induces renal epithelial cell death. To further substantiate a direct effect of transgene expression, we transplanted kidneys between normal and transgenic mice. Transgenic mice with 2+ proteinuria received a transplant from a normal littermate and transgenic kidneys with 2+ proteinuria were transplanted into normal mice. At the time of transplant, both native kidneys were removed. HIV-associated nephropathy developed in transgenic kidneys transplanted into normal mice. Normal mice that received transgenic kidneys have remained apparently normal. Thus, the renal disease in the murine model is intrinsic to the kidney and not a response to the systemic "milieu" or to expression from a distant site. These studies suggest that in man, a direct effect of HIV-1 expression is likely the essential cause of HIVAN.

Immunolocalization Using Antibodies Raised against a Renal Brush Border Oligonucleotide Channel. B. Hanss, E. Leal-Pinto, N. Tulchin, S. Dikman, and P. Klotman, Departments of Medicine and Pathology, Mount Sinai School of Medicine, New York, NY.

Many cells are capable of responding to and degrading DNA yet the mechanism for nucleic acid uptake into cells remains poorly defined. We have purified a DNA-binding protein from renal brush border membrane that functions as a highly selective single-stranded DNA conducting channel when reconstituted in artificial lipid bilayers. Polyclonal antibodies directed against two synthetic peptides derived from preliminary amino acid sequence data were generated. Antisera from two peptides were positive in enzyme-linked immunosorbent assay for antigen polypeptide at a 1:10,000 dilution and recognized the DNA-binding protein by Western blot analysis. Both antibodies blocked DNA-activated gated channel activity in lipid bilayer experiments by more than 90% at a dilution of 1:100. These antisera were then used in immunohistochemical analysis of tissues known to accumulate oligonucleotides. Adult rats were sacrificed and kidney, liver, and spleen were harvested and frozen in liquid nitrogen. Antibody detection (at 1:100) was performed using a biotinylated goat anti-rabbit secondary antibody and horseradish peroxidase-labeled streptavidin (Dako Inc.). Within the kidney, both antibodies localized to proximal apical membrane. Distal tubules were also immunoreactive; however, glomeruli, thin ascending and descending limbs, the collecting system, and the renal vascular tree were not immunoreactive. Within the liver, intense staining was confined primarily to bile duct epithelium but hepatocytes exhibited diffuse low-intensity staining as well. Immunoreactivity was also observed in spleen and appeared to be limited to one or two cell types. These studies suggest that the antibodies directed to the renal DNA channel also recognize the other tissues that are known to accumulate oligonucleotides. Thus, the mechanism for nucleic acid uptake in liver, splenocytes, and kidney may share antigenic features.

The Development of a Ribozymes as a Therapeutic Approach for Polycystic Kidney Disease. J. Hu,[1] P. Wilson,[2] P. Klotman,[2] and J. Rappaport.[2] [1]Stuyvesant High School/Westinghouse Program and [2]Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Polycystic kidney disease (PKD) affects more than 5 million people worldwide. PKD is an inherited disease, ultimately requiring dialysis and/or kidney transplantation. Both autosomal dominant (ADPKD) and autosomal recessive (ARPKD) inheritance patterns are found in families with PKD, suggesting distinct mechanisms of renal pathogenesis. ADPKD is the more common form of the disease, affecting 1 in 400 to 1 in 1,000 persons.

Two genes have been identified which are mutated in patients with ADPKD (PKD-1 and PKD-2). It is unknown whether these mutations lead to a loss of function or a gain of function, and the mechanism of pathogenesis is unclear. The PKD-1 gene is silent in normal adult kidney, but highly expressed in PKD renal tissue. This might suggest that the abnormal expression of the mutant PKD-1 protein leads to dysregulation of renal gene expression. Molecular approaches designed to reduce PKD-1 mRNA might be beneficial in restoring normal regulatory status.

Ribozymes are RNA molecules that can bind, by Watson-Crick base pairing, to target RNA and to carry out catalytic cleavage. We have designed a ribozyme to cleave one of the potential target sites in PKD-1 mRNA. Cleavage analysis was performed using *in vitro* synthesized ribozyme and substrate RNAs of varying lengths. The results suggest that a ribozyme containing six base pairs in helix-1 provides the optimal cleavage activity. Future studies will investigate the effect of expressed ribozyme in cells derived from polycystic kidneys. A ribozyme targeted to PKD-1 mRNA may serve as potential therapeutic agent in polycystic kidney disease and may be a useful tool for determining the role of mutant PKD-1 in renal pathogenesis.

Roles for Retinoic Acid and Midkine in Proximal Tubule Epithelial Differentiation During Renal Development. D. P. Hyink, C. R. Burrow, and P. D. Wilson. Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Important soluble mediators of mesenchymal to epithelial conversion that may be active in renal development include retinoic acid (RA) and midkine (MK), a RA-induced, kidney-specific, secreted heparin-binding growth factor. Induction of the metanephric mesenchyme *in vivo* is characterized by formation of cellular aggregates of condensing cells associated with the transcriptional activation of Pax-2, WT-1, and E-cadherin and switching of $\alpha 8$- to $\alpha 9$-integrin expression. MK is expressed in metanephric blastemal cells and exclusively in the proximal tubule epithelia of adult kidneys. Our previous studies have shown that RA and MK induce a subpopulation of cultured human renal progenitor cells to differentiate into epithelial foci. Because Wilms' tumors (WT) are derived from blastemal cells of the metanephric kidney, we have now studied the RA- and MK-responsive WT cell line SK-NEP1 which display an *in vitro* induction of cellular aggregation similar to the initial cellular events of nephron induction *in vivo*. In the absence of stimulus, SK-NEP-1 cells grow as a monolayer, but after addition of RA or homogeneously purified MK numerous free-floating, multicellular aggregates are formed after 12 hours, which on electron microscopy contain tight cell-cell adhesion, desmosome formation, and small lumens. Pleiotrophin (PTN), a heparin-binding growth factor homolog of MK, which is not not kidney-restricted, showed no effect on aggregate formation:

		RA µM			MK ng/mL			PTN ng/mL
Treatment	Vehicle	0.005	0.01	0.1	0.5	1.0	2.5	1–10
Aggregates (number)	2	86	227	234	41	33	29	3

Molecular targets of condensate induction were identified using immunohistochemistry and Western blot analysis before and after MK- and RA-induced conversion. Uninduced monolayers expressed WT-1 and α9-integrin, whereas aggregates expressed α8-integrin and Pax-2. Ongoing studies point to this inducible SK-NEP-1 cell culture model as a suitable system to analyze transcriptional control of epithelial conversion of mesenchymal cells in nephrogenesis.

Effect of Urea and Counteracting Osmolytes on Sodium-Potassium Cotransporter Thick Ascending Limb. D. M. Kaji, J. C. Parker, and J. Diaz. Division of Nephrology, Department of Medicine, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

The concentration of urea increases in the renal medulla along the corticopapillary axis so that the inner medullary urea concentrations (500 mM in mammalian kidneys) are substantially higher than blood urea concentrations (2–3 mM). We have previously reported that urea in subdenaturing concentrations alters ion transport in human erythrocytes. However, the effect of urea on renal medullary cells has not been examined. We examined the effect of physiological concentrations of urea (100–500 mM) on NaK_2Cl cotransport in cultured cells from mouse medullary thick ascending limb (mTAL). K influx was measured with ^{86}Rb uptake over 3 min. Urea acutely inhibited bumetanide-sensitive K influx in mTAL cells in a concentration-dependent fashion, with a statistically significant inhibition (19%) at 100 mM, and 86% inhibition at 500 mM. The effect of urea was entirely reversible and was blocked by prior treatment with okadaic acid, a phosphatase inhibitor, suggesting that urea exerts its action upstream of the phosphorylation-dephosphorylation step. Cell volume was unchanged in the presence of 500 mM urea. The number of [^3H]bumetanide binding sites, a mesaure of the number of functioning cotransporter sites, was decreased in the presence of urea, and the decrease in bumetanide binding was proportional to the decrease in bumetanide-sensitive K influx. Urea also stimulated the Ba-sensitive, swelling-activated K efflux from mTAL cells. Growing the cells in hyperosmolar media high in urea (250 mM) did not alter ion transport in the simultaneous presence of betaine and glycerophosphocholine, suggesting that these osmolytes counteracted the chronic effect of urea. However, further acute addition of 250 mM urea (final urea concentration, 500 mM) decreased the bumetanide-sensitive ion transport by nearly 50%, suggesting that counteracting osmolytes protect against the chronic high ambient urea concentrations, but may not protect adequately during disequilibrium when urea concentrations are rising rapidly. Thus, urea, in concentrations that prevail in the renal medulla, inhibits NaK_2Cl cotransport and stimulates Ba-sensitive K efflux in thick ascending limb cells. These effects may modulate salt transport in the thick limb during conditions when urea concentrations are rising rapidly (dehydration, vasopressin stimulation, or high protein feeding).

Genistein Inhibits NaK_2Cl Cotransport in Human Erythrocytes. D. M. Kaji. Division of Nephrology, Department of Medicine, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

The NaK_2Cl cotransport has been shown to play an important role in volume regulation of human erythrocytes. Little is known about the regulation of this transport pathway in the human erythrocyte. We examined the role of protein kinases in the acute regulation of NaK_2Cl cotransport activity (NaK_{cot}) in the human erythrocytes. NaK_{cot} was measured as the ouabain-resistant K influx that was inhibitable by 2 µM bumetanide in media containing 145 mM NaCl, 5 mM KCl, and tracer ^{86}Rb. RpcAMP, a specific cAMP disastereomer that competitively inhibits cAMP-dependent protein kinase (PKA), and agents that stimulate PKA, including forskolin, 8-Br-cAMP, and CPT-AMP, were all without effect on bumetanide-sensitive K influx. Similarly, several protein kinase activators, such as phorbol esters, and inhibitors such as sphingosine and chelerythrine were without effect on bumetanide-sensitive K influx. In contrast, genistein, a tyrosine kinase inhibitor, decreased NaK_{cot} significantly. Nearly 90% of the cotransport was inhibited by 200 µM genistein, and the concentration required for half-maximum inhibition was 18 to 26 µM in cells from three different donors. Two other inhibitors of tyrosine kinase, lavendustin A, and methyl 2,5-dihydroxycinnamate (a stable analog of erbstatin) were also effective in inhibiting NaK_{cot}; however, tyrphostin, a more selective tyrosine kinase inhibitor, which inhibits epidermal growth factor receptor kinase but not insulin receptor kinase, had no inhibitory effect on cotransport. The inhibitory effects of genistein were blocked by prior exposure to 1 mM vanadate, a nonspecific inhibitor of tyrosine phosphatase. These results suggest an important role for tyrosine kinase in the regulation of NaK_{cot} in human erythrocytes.

Supported by Merit Review Grant, Veterans Affairs General Medical Research.

Transduction of Renal Cells *In Vitro* and *In Vivo* by Adeno-Associated Virus Gene Therapy Vectors. M. S. Lipkowitz, B. Hanss, N. Tulchin, P. D. Wilson, G. J. Kurtzman, P. E. Klotman, and M. E. Klotman. Divisions of Nephrology and Infectious Diseases and Department of Pathology, Mount Sinai School of Medicine, and Avigen Inc.

Adeno-associated virus (AAV) is a defective parvovirus with unique properties making it an attractive vector for renal gene delivery: wild-type virus integrates into restricted sites in the host chromosome, does not require cell division for transduction, and results in long-term expression of delivered genes. We have previously shown transduction of primary and immortalized mesangial cells in culture, and that transduction can be enhanced by pretreatment of cells with cisplatinum. The current studies were designed to further assess pharmacologic enhancement of mesangial cell transduction, transduction of cultured human renal tubule cells, and transduction of mouse kidney *in vivo*.

Normal human mesangial cells (NHMC) were pretreated for 16 hours with vehicle, 1 µM cisplatinum, 40 mM hydroxyurea, 1 µM etoposide; 1 µM camptothecin, or 5 mg/mL aphidicolin, and exposed to recombinant AAV containing the lacZ reporter gene with a cytomegalovirus promoter (rAAVlacZ) at a multiplicity of infection of 0 1 infectious viral particles per cell. Primary human proximal tubule (PT), thick ascending limb (TAL) and collecting tubule (CT) cells grown to confluence on collagen were exposed to rAAVlacZ for 48-hours, then stained by β-Gal activity. For *in vivo* studies, right mouse kidneys were exposed via a flank incision and injected with 4×10^3 infectious viral particles rAAVlacZ per injection site. Animals were sacrificed 7 days postinjection and kidney sections were stained for β-Gal activity.

Transduction efficiencies for PT, TAL, and CT were similar to that for NHMC. Pharmacologic pretreatment of NHMC with chemotherapeutic agents resulted in at least a 4- to 6-fold enhancement of transduction by rAAVlacZ. Intraparenchymal infection resulted in transduction of epithelial cells in the vicinity of the injection site with an efficiency of 5 to 10%.

These studies provide evidence that recombinant AAV can transduce a broad variety of renal tubule cell types both *in vivo* and *in vitro*, and is therefore a potentially important vector for intrarenal gene delivery. Furthermore, there is potential for enhancement of AAV-mediated gene delivery, as transduction efficiency *in vitro* can be increased significantly by pharmacologic agents at doses currently approved for use *in vivo*.

The RNA Component of Human Telomerase as a Potential Target for Cancer Therapy. L. Miller, P. E. Klotman, and J. Rappaport.[2] [1]Hunter College High School, Westinghouse Program and [2]Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Chromosomal ends (telomeres) consist of thousands of repeats of the sequence TTAGGG (in humans). During the process of DNA replication, telomeric sequences are lost. In normal somatic cells, telomeric sequences continue to shorten with progressive cellular division and normal aging. When telomeres become critically short, cells enter senescence. Although this process appears to ensure our ultimate mortality, it provides a checkpoint for excessive cellular replication and may be protective in tumorigenesis. Certain malignant tumor cells, however, have activated the enzyme telomerase, the ribonucleic acid-protein complex responsible for extending telomeric repeats. Strategies designed to inhibit telomerase enzyme activity might be beneficial in limiting the replicative capacity of malignant cells.

As a therapeutic approach we have designed a hairpin ribozyme directed to the RNA component of human telomerase. Ribozymes are RNA molecules derived from plant viroids with the capacity to cleave RNA. Currently the ribozyme is being tested to optimize catalytic activity *in vitro*. Once the optimum configuration has been determined, the ribozyme will be introduced into transformed cell lines and be analyzed for its efficacy.

Ribozymes as Potential Therapeutic Agents for the Treatment of Renal Diseases: in Vitro Activity of Transforming Growth Factor-β Targeted Ribozymes. J. Rappaport,[1] M. W. Richardson,[1] A. Hampel,[2] and P. E. Klotman.[1] [1]Division of Nephrology, Mount Sinai School of Medicine, New York, NY and [2]Northern Illinois University, Dekalb, IL.

Transforming growth factor-β (TGF-B) is a potent regulator of cell proliferation and gene expression. TGF-β1 is synthesized locally in the kidney by glomerular mesangial cells and tubule epithelial cells, providing a potential mechanism for renal pathogenesis. TGF-β1 induces the synthesis of matrix proteins (i.e., collagens, fibronectin, heparin sulfate proteoglycans) and integrins. TGF-β is elevated in various renal disease states including antiglomerular basement membrane disease, lupus nephritis, Masugi nephritis, and in human immunodeficiency virus-associated nephropathy. As a first step toward therapeutic reduction in TGF-β mRNA levels, we have identified sequences within human and murine TGF-β-1 mRNA, predicted to serve as substrates for engineered hairpin ribozymes.

Ribozymes are RNA molecules derived from plant viroids which can cleave mRNA. The "hammerhead and hairpin," two ribozyme prototypes which have been used in gene therapeutic strategies, can be adapted to cleave various target mRNAs. For cleavage by the hairpin ribozyme, substrates must contain the consensus sequences bNGUC, where N is any base and b cannot be an A. We have designed and demonstrated the activity of hairpin ribozymes directed to human and mouse TGF-β-1 mRNA in a cell-free system containing *in vitro* synthesized ribozyme and substrate RNAs. RNA cleavage assays were performed to determine kinetic properties and to optimize *the vitro* cleavage reaction. K_{cat} and K_M estimates were deduced by nonlinear regression analysis of data obtained from cleavage reactions containing varying amounts of RNA substrate. Future studies in cell culture will determine the efficacy of targeted ribozymes in reducing TGF-β-1 mRNA in renal cell types.

Potential Role for Midkine in Autosomal Dominant Polycystic Kidney Disease Cyst Formation. S. Serebnitsky, D. P. Hyink, and P. D. Wilson. Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, NY.

Fifty percent of autosomal dominant polycystic kidney disease (ADPKD) patients who inherit the *PKD-1* mutation progress to end-stage renal failure necessitating dialysis or transplantation. At present, there are no therapies available to slow down the rate of renal cyst expansion associated with progression to renal failure. Cell biological and physiological studies from our and other laboratories have established that the pathogenesis of cyst formation in ADPKD occurs as the result of abnormal tubule epithelial cell proliferation (hyperplasia) by every tubular segment of the nephron and fluid accumulation caused by ion and fluid secretion into the lumen of cysts. Midkine (MK) is a heparin-binding growth factor that increases the rate of cell proliferation in the Wilms' tumor line G401 and promotes epithelial differentiation of renal progenitor cells. During development, MK localizes to sites of mesenchymal-epithelial interactions, including the fetal kidney whereas in the adult, MK expression is restricted solely to the kidney proximal tubule. In ADPKD kidneys, *in situ* and immunolabeling analysis demonstrated that MK mRNA and protein localized to the epithelial cells lining the cysts. We examined cyst fluids from ADPKD kidneys and supernatants from cultures of primary and clonal lines of proximal tubule and ADPKD cells for secreted MK by slot-blot and Western analysis. The blots were probed with biotinylated goat-anti-human MK (R&D Systems) and showed a high level of secreted MK in PKD cyst fluid and in three separate primary ADPKD cell lines. These results suggest that in ADPKD kidneys, MK is secreted into the cyst fluid and could potentially affect the rate of cystic epithelial proliferation.

Free Intracellular Magnesium is Not Elevated in Patients with Chronic Renal Failure on Dialysis. W. Shilkoff and D. Kaji. Division of Nephrology, Department of Medicine, Bronx VA Medical Center and Mount Sinai School of Medicine, New York, NY.

Elevated Mg has been proposed to play a role in the pathophysiology of uremia. Chronic renal failure (CRF) has been found to be associated with hypermagnesemia and elevated total Mg content of tissues. However, regulation of cellular functions depends on the intracellular free Mg concentration ($[Mg]_i$), rather than the total tissue Mg. $[Mg]_i$ has not been determined in patients with CRF or in animal models of CRF.

In the present study, we examined the predialysis plasma total Mg and free intracellular Mg in 20 patients with CRF (18 patients receiving hemodialysis with a dialysate Mg of 0.37 mM and 2 receiving continuous ambulatory peritoneal dialysis. Ten subjects with normal renal function served as controls.

Free intracellular Mg was determined in polymorphonuclear leukocytes (PMNL) using the ratiometric fluorescent dye furaptra. Ten to twenty measurements were made for each subject, with each measurement derived from two to three PMNLs. Mean total plasma MG was normal in CRF patients (1.9 ± 0.5 mg/dL or 0.79 ± 0.21 mM), but three patients had frank hypermagnesemia at the time of the study. PMNL $[Mg]_i$ was 0.57 ± 0.07 mM in CRF patients versus 0.54 ± 0.06 mM in controls (NS). $[Mg]_i$ was also not elevated in the three hypermagnesemic patients (0.59 ± 0.03 mM). $[Mg]_i$ was not correlated with serum total Mg, total Ca or parathyroid hormone levels.

Thus, patients with CRF maintain their ability to regulate $[Mg]_i$. We find no evidence to support the role of elevated $[Mg]_i$ in the neurological and other abnormalities of uremia.

Coexpression of the *PKD-1* Protein with Matrix Receptor and Adhesion Plaque Proteins in Human Fetal and Autosomal Dominant Polycystic Kidney Disease Epithelia *In Vitro*. P. D. Wilson and C. R. Burrow. Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Human autosomal dominant polycystic kidney disease (ADPKD) is caused by a mutation in the *PKD1* gene, which leads to aberrant renal tubule epithelial cell proliferation and lumenal fluid secretion into multiple cysts. Several features of ADPKD cells suggest a fetal phenotype and *PKD-1* mRNA and protein (polycystin) are highly expressed in the ureteric bud during early human nephrogenesis and in ADPKD cystic epithelia, but down-regulated in normal adult kidneys. Primary and immortalized epithelial cell cultures have been established from normal human fetal and adult renal proximal tubules, thick ascending loops of Henle and collecting tubules as well as from ADPKD cyst-lining epithelial cells. Using a riboprobe (psp 7213.1) against the last 3′-exon and a polyclonal peptide antibody (ID2154) against a corresponding 30-amino acid portion of the polycystin C-terminal, *in vivo* and *in vitro* analysis show that *PKD1* mRNA and protein are most highly expressed in ADPKD cyst epithelia as well as in human fetal collecting tubule epithelia. Moderate expression of *PKD1* was seen in normal adult collecting tubules and fetal proximal tubule epithelia, whereas normal adult proximal tubule and thick ascending limb epithelia were negative. Adhesion assays were carried out *in vitro* and ADPKD epithelia shown to be the most adherent cell type > fetal collecting tubules > adult collecting tubules > adult proximal tubules and thick ascending limbs, suggesting a correlation between *PKD1* mRNA and polycystin content and degree of adherence. ADPKD epithelia were most adherent to the matrix protein type I collagen > type IV collagen > fibronectin > laminin. Immunostaining analysis showed that in normal cells, polycystin was most frequently associated with the cell membrane. In ADPKD cyst epithelial cells, however, polycystin was not only quantitatively up-regulated but also localized to additional cytoplasmic sites. Colocalization studies using antipolycystin, vinculin, $\alpha 2\beta 1$ integrin, focal adhesion kinase (pp125^{FAK}) and pp60^{src} antibodies suggest involvement of polycystin in focal adhesion plaque formation in adherent ADPKD and fetal collecting tubule cells.

Plasma Human Immunodeficiency Virus-1 RNA in Seropositive Patients with Renal Disease. J. Winston, P. E. Klotman, M. Klotman*. Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

In human immunodeficiency virus-1 (HIV-1)-seropositive patients, plasma viral load correlates best with progression to acquired immunodeficiency syndrome (AIDS) and is a better indicator of progression than peripheral CD4 count. Although renal disease is not considered an AIDS-defining condition, we hypothesized that HIV viral burden may correlate with the development of HIV-associated nephropathy (HIVAN). In addition, because HIV+ patients receiving dialysis have a high mortality rate which correlates with progression to AIDS, we examined whether viral burden is higher after the onset of dialytic therapy.

We measured HIV-1 RNA copy number in patients with biopsy-proven HIVAN before they required chronic dialysis and in HIV+ patients already receiving dialysis. Plasma HIV-1 RNA was measured with a quantitative-competitive reverse transcription polymerase chain reaction assay (Amplicor, Roche). We found that before the initiation of dialysis, RNA copy number was 3,539 ± 2,880 (mean ± SEM). In contrast, patients already receiving dialysis had a copy number of 103,140 ± 37,100. These data suggest that high viral burden is not associated with the development of HIVAN. But, progression to AIDS on dialysis may be related to increased viral replication. We conclude that viral burden alone does not explain the development of HIVAN in patients at risk. In addition, the process of dialysis may stimulate viral replication and interventions that reduce viral replication may lead to longer survival on dialysis.

Cloning of cAPK-δ, A Novel Serine/Threonine Kinase from Human Fetal Kidney. C. Wong, S. J. Wilson, C. R. Burrow, and P. D. Wilson. Division of Nephrology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Protein kinases are tissue- and temporally restricted during development and differentiation. Human fetal renal development and polycystic kidney disease (PKD) epithelia are characterized by proliferation and secretion, whereas normal adult renal epithelia *in vivo* are postmitotic. A degenerate polymerase chain reaction (PCR)-cloning strategy was used to investigate the role of serine/threonine kinases in renal proliferative pathways. Degenerate primers were designed for amplification of protein kinase C (PKC) and PKA-related genes and reverse transcription (RT)-PCR carried out using RNA isolated from human fetal kidney and normal adult kidney as well as from autosomal dominant (AD) and autosomal recessive (AR)PKD kidneys. A novel serine/threonine kinase was cloned and sequenced which showed 78% amino acid identity to DC-2, a developmentally regulated Drosophila cAMPK-related gene; 67% identity to human cAMP-PKA and only 63% homology to human PKC-δ in the catalytic domain. We have called this new kinase cAPK-δ. RNase protection analysis showed differential expression in human fetal, ADPKD, and ARPKD kidneys. No expression was detected in normal adult kidneys. Using a digoxygenin-labeled riboprobe, *in situ* hybridization localized cAPK-δ to the ureteric bud and collecting tubules of human fetal kidneys (8–17 weeks gestation) and in the cyst-lining epithelial cells of ADPKD and ARPKD kidneys. No localization was detected in normal adult kidneys. Identical differential patterns of expression of cAPK-δ were seen in primary cultures and immortalized clonal cell lines derived from human renal epithelia. Fetal collecting tubules and cyst-lining ADPKD and ARPKD epithelia were positive whereas fetal and adult proximal tubules and adult collecting tubules and thick ascending limb epithelia were negative. Our previous biochemical and cell biological studies have suggested hyperphosphorylation of protein kinases as well as cAMP-mediation of epithelial cell proliferation and secretion in ADPKD. We conclude that cAPK-δ is a novel protein kinase in proliferating renal epithelial cells and seek to define its role in the mitogen-induced signal transduction cascade.

Supported by National Institutes of Health RO1 DK40698.

Spinal Cord Research

Airway Hyperreactivity in Subjects with Spinal Cord Injury Is Not Reversed by Lung Inflation. P. L. Almenoff, R. V. DeLuca, M. Lesser, D. R. Grimm, A. M. Spungen, W. A. Baumann. Spinal Cord Damage Research Center, Bronx VA Medical Center, Divisions of Pulmonary Medicine and Endocrinology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Bronchial hyperresponsiveness to methacholine (M) and histamine (H) has been demonstrated previously in subjects with chronic cervical spinal cord injury (SCI). This syndrome was attributed to loss of sympathetic airway innervation, resulting in unopposed parasympathetic (bronchoconstrictor) activity. However, recent findings suggest that airway hyperresponsiveness in subjects with SCI may be caused by inadequate stretch of airway smooth muscle because of inability of the subjects to inhale deeply. In support of this theory, it has been shown that normal individuals transiently decrease airway resistance with deep aspiration following M- or H-induced bronchoconstriction, whereas no decrease occurs in asthmatic subjects under the same conditions. Therefore, we determined whether lung inflation reverses M- or H-induced bronchoconstriction in subjects with cervical SCI. Subjects inhaled M or H in increasing concentrations until a 20% decrease in forced expiratory volume in 1 S (FEV$_1$) from baseline was observed (PC$_{20}$). The mean PC$_{20}$ and %Δ in FEV$_1$ for M or H are shown below. Immediately after administration of the last dose of M and H, and without provision of a bronchodilator, a volume-cycled ventilator (Life Care PLV-102) was used to administer eight breaths at a volume between 60 and 70% of the baseline forced vital capacity, the maximum amount tolerated by the subjects. Immediately after lung inflation, spirometry was repeated. The results are expressed as mean ± SD.

Drug	n	PC_{20}	FEV1[a]	FEV1[b]
M	3	1.43 ± 1.47	24 ± 4%	26 ± 9%
H	7	1.92 ± 1.30	40 ± 9%	35 ± 15%

[a] % decrease from baseline after challenge.

[b] % decrease from baseline after challenge and lung inflation.

These data reveal that lung inflation did not reverse M- or H-induced bronchoconstriction in the subjects. The findings suggest that airway smooth muscle in subjects with cervical SCI fails to stretch normally with deep inhalation, possibly because of microatelectasis associated with chronic restrictive ventilatory defect. Alternatively, the volumes used in the study, which were the maximum amounts tolerated by the subjects, may have been of insufficient volume or duration to overcome bronchoconstriction induced by methacholine or histamine.

A Comparison of Bone Density in Monozygotic Twins: One with Spinal Cord Injury. W. A. Bauman, A. M. Spungen, J. Wang, and R. N. Pierson, Jr. Spinal Cord Damage Research Center, Bronx VA Medical Center; Division of Endocrinology, Department of Medicine, Mount Sinai School of Medicine, New York, NY; The Body Composition Unit, Columbia-St. Luke's/Roosevelt Hospital Center, New York, NY.

This study determined the magnitude and the effect of duration of paralysis, rather than age, on the loss of bone mineral density (BMD) in those regions of the skeleton most influenced by spinal cord injury (SCI). The design consisted of a two group (SCI and nonSCI) matched sample. Seven pairs of identical twins confirmed by genetic testing, one twin having SCI, were studied. The mean age and height of the total group was 37 ± 7 years and 175 ± 10 cm. The mean weight for SCI and nonSCI were 65.6 ± 9.7 and 74.6 ± 15.3, $p < 0.05$, respectively. Duration of injury for the SCI group was 11 ± 10 years (range, 2–27 years). Total and regional BMD were measured by dual photon x-ray absorptiometry (Lunar Model DPX, Madison, WI). The results are reported as mean ± SD and g/cm^2.

	TBD	Arms	Legs	Pelvis	Spine
SCI twin	1.09	1.014	0.936*	0.963*	1.304*
	±0.027	±0.068	0.135	±0.169	±0.097
NonSCI twin	1.26	1.006	1.409	1.238	1.181
	±0.030	±0.051	0.106	±0.107	0.080

BMD was significantly reduced in the group with paraplegia for the pelvis and legs. Linear regression analyses revealed strong linear correlations between duration of injury and the difference between twin pairs for total body bone mass ($r = 0.96$, $p = 0.0007$), total bone density (TBD) ($r = 0.85$, $p = 0.015$), leg BMD ($r = 0.85$, $p = 0.015$), and pelvis BMD ($r = 0.83$, $p = 0.02$). There was no significant correlation between age and bone mass or bone mineral density measurements.

In summary, the twins with paraplegia compared with their identical co-twins: (1) BMD below the level of injury (i.e., leg and pelvis) was reduced by about 35% and (2) BMD above the level of injury was not significantly different in the arms but was significantly increased in the spine. Duration of injury, not age, was a strong predictor of bone loss in the twin with SCI. Because of the opportunity to have a nonSCI twin to compare with an SCI co-twin, it was possible to demonstrate for the first time that bone loss is related to duration of injury, refuting the general assumption that bone loss occurs almost exclusively during the first 6 to 12 months after paralysis. Thus in patients with chronic SCI, therapeutic intervention should prove to be efficacious to prevent further bone loss and to reduce the risk of fractures, with its associated morbidity and mortality.

Prevalence of Sleep-Related Complaints in Subjects with Chronic Spinal Cord Injury. D. R. Grimm, A. M. Spungen, W. A. Bauman, M. Lesser, P. L. Almenoff. Spinal Cord Damage Research Center, Bronx VA Medical Center, Bronx, NY; Divisions of Pulmonary Medicine and Endocrinology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

A lack of information exists regarding the prevalence of sleep-related complaints in the population with spinal cord injury (SCI), even though our current knowledge regarding evaluation and treatment of these disorders has improved greatly. Recent studies have shown that a significant number of subjects experience arterial oxygen desaturation during sleep, along with apnea. Because the incidence of sleep-related complaints in subjects with SCI has not been reported, difficulty in assessing the clinical relevance of the complaint(s) of an individual patient are without objective context. The purpose of this study, therefore, was to determine the prevalence of sleep-related complaints in a group of healthy outpatient male veterans with chronic SCI. We collected data using a sleep history questionnaire, modified for SCI, from 54 subjects (30 with quadriplegia and 24 with paraplegia), whose duration of injury exceeded 1 year. Thirty two (59%) of the subjects questioned reported frequently experiencing three or more sleep-related complaints. Subjects with greater body weight (81.4 ± 16 vs 69.2 ± 12 kg; $p < 0.008$) reported significantly more complaints than those reporting fewer than three. There were no significant differences, however, between subjects with quadriplegia and paraplegia for any reported complaint. We compared our findings with those obtained in a previous study, based on the 1970 census of a stratified sample ($N = 1006$) that examined the prevalence of sleep disorder complaints in able-bodied persons in the Los Angeles (LA) metropolitan area.

Question	Quadriplegia[a]	Paraplegia[a]	LA study[a]
Habitual snorer	20 (66.7)	14 (58.3)	186 (18.5)
Daytime hypersomnolence	10 (33.4)	14 (58.3)	71 (7.1)
Difficulty falling asleep	12 (40.0)	12 (50.0)	235 (23.4)
Midsleep awakenings	13 (43.3)	12 (50.0)	271 (26.9)
Early morning awakenings	9 (30.4)	9 (37.5)	172 (17.1)
Feel tired, disoriented/foggy	6 (20.1)	7 (29.2)	–
Gasping/difficulty breathing upon awakening	8 (26.7)	3 (12.5)	–

[a] Number of subjects (percent).

Our findings demonstrate that a greater percentage of subjects with chronic SCI report sleep-related complaints than the general population. Awareness of the high prevalence of sleep-related complaints in this population may aid the clinician in more effectively addressing and treating sleep apnea and hypopnea.

Reduced Baroreflex Sensitivity Index in Patients with Spinal Cord Injury. D. R. Grimm, R. E. De Meersman, W. A. Bauman, and P. L. Almenoff. Spinal Cord Damage Research Center, Bronx VA Medical Center; Divisions of Pulmonary Medicine and Endocrinology, Department of Medicine, Mount Sinai School of Medicine, New York, NY; Department of Rehabilitation Medicine, College of Physician and Surgeons, Columbia University, New York, NY.

The Valsalva maneuver (VM) is widely used to assess baroreflex sensitivity (BRS) and parasympathetic function. A reduced BRS primarily reflects an impairment in the vagal efferent component of the baroreceptor reflexes, and patients with essential hypertension have been shown to exhibit decreased BRS. In 1989 Yekutiel and colleagues demonstrated that the incidence of hypertension and ischemic heart disease was significantly increased among patients with spinal cord injury with a duration exceeding 10 years, when compared with able-bodied, age-matched controls. The purpose of this study was to use Phase 4 of the VM to assess BRS in patients with spinal cord injury (paraplegia). Ten healthy normotensive subjects participated in this study: five with paraplegia and five able-bodied controls. Heart rate and blood pressure were measured beat-to-beat by use of lead II of the electrocardiograph and finger photoplethysmography; data were digitized, recorded, and stored on hard disk for later analysis. Subjects began by resting quietly for 30 minutes, after which 3 minutes of data were collected for baseline measures. The VM was performed by having subjects blow into a mouthpiece, connected by a tube to a manometer, sustaining a total pressure of 40 mm Hg over 15 seconds; this procedure was repeated three times. Phase 4 of the VM was calculated starting with the lowest systolic peak of the arterial pressure rise plotted against the first beat with a lengthened R-R interval. A linear regression analysis was performed and a final slope was calculated using at least five points. Only regression lines with a correlation coefficient greater than 0.80 were accepted for analysis. A one-way ANOVA with *post hoc* analysis was conducted using Scheffe pairwise comparisons ($p < 0.05$); data are expressed as mean ± SEM. No significant differences between groups were observed for age, baseline heart rate variability, or systolic blood pressure variability. A reduced BRS index was observed in the patients with paraplegia, 2.36 ± 0.97 ms/mm Hg, compared with controls, 8.1 ± 0.95 ms/mm Hg ($p < 0.002$). BRS values below 3.0 ms/mm Hg represent a depressed response. These findings support previous work in which patients with paraplegia were found to have an increased incidence of hypertension, and suggest that reduced BRS may be considered as a precursor of overt clinical hypertension.

Thrombin-Induced Release of Platelet-Derived Growth Factor Is Elevated in Spinal Cord Injury and Normalized by Verapamil. N. N. Kahn, R.-L. Zhang, W. A. Bauman, and A. K. Sinha. Spinal Cord Damage Research Center, Bronx VA Medical Center; Department of Medicine, Mount Sinai School of Medicine, NY.

Studies of subjects with chronic spinal cord injury (SCI) have shown a significant increase of premature coronary artery disease (CAD) when compared with nonSCI individuals. The underlying mechanism remains obscure. Because platelet-derived growth factor (PDGF), a mitogen, is well known for its appreciated critical role in the development of atherosclerosis through focal smooth muscle cell proliferation, we investigated the status of PDGF and its release by thrombin in the circulation in SCI subjects ($n = 8$) compared with nonSCI controls ($n = 8$). PDGF levels were assayed by an enzyme-linked immunosorbent assay system. It was found that the basal plasma PDGF level in those with SCI was three times higher (6.41 ± 0.12 ng/mL) than nonSCI controls (2.15 ± 0.12 ng/mL). The thrombin-induced release of PDGF in SCI was also persistently higher (24.2 ± 1.2 pg/10^6 cells) when compared with nonSCI controls (15.11 ± 1.6 pg/10^6 cells) under identical conditions. The pretreatment of SCI platelets with 100 nM prostaglandin E_1 (PGE_1) (used as a stable probe of prostacyclin) inhibited the release of the mitogen by 90% ($p < 0.001$) in nonSCI control platelets. In contrast, similar treatment of platelets from SCI subjects had no such affect.

The inability of PGE_1 to reduce PDGF release to normal may be related to the loss of high-affinity prostacyclin receptors on the platelet surface and might be responsible for the increased plasma level of PDGF in those with SCI. On the other hand, pretreatment of SCI platelets with 10 μM verapamil, a calcium ion channel blocker, "corrected" the release of PDGF to "normal" ranges ($p < 0.001$). These results suggest that the use of a calcium ion channel blocker, such as verapamil, might be beneficial in those with SCI by correcting the excessive release of PDGF to normal, thus potentially ameliorating the deleterious effect on the vasculature.

Correlation of Respiratory Symptoms with Smoking History and Completeness of Injury. M. Lesser, D. R. Grimm, A. M. Spungen, W. A. Bauman, P. L. Almenoff. Spinal Cord Damage Research Center, Bronx VA Medical Center, Divisions of Pulmonary Medicine and Endocrinology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

In the current study, we evaluated the prevalence of respiratory symptoms in current smokers, exsmokers (Ex-SMK, ≥1 year), or never smokers with spinal cord injury and in subjects with complete or incomplete motor lesions (completeness of injury) by administering a standard respiratory questionnaire modified for subjects with spinal cord injury. We found that respiratory symptoms were unrelated to smoking status in subjects with quadriplegia, whereas complaints of phlegm and wheeze were significantly more prevalent in currently smoking subjects with paraplegia as compared with never smokers, and phlegm was also more prevalent in current smokers as compared with exsmokers. The prevalence of respiratory symptoms in subjects with quadriplegia and paraplegia was unrelated to completeness of motor injury.

	Quadriplegia[a]		
	Current ($n = 80$)	Ex-SMK ($n = 28$)	Never ($n = 29$)
Breathlessness	67 (20)	61 (17)	62 (18)
Cough	20 (6)	11 (3)	21 (6)
Phlegm	37 (11)	31 (9)	21 (6)
Cough and phlegm	27 (8)	21 (6)	24 (7)
Wheeze	40 (12)	29 (8)	21 (6)
Any Symptom	83 (25)	75 (21)	69 (20))

	Paraplegia[a]		
	Current ($n = 30$)	Ex-SMK ($n = 40$)	Never ($n = 23$)
Breathelessness	40 (12)	35 (14)	26 (6)
Cough	33 (10)[b]	15 (6)	9 (2)
Phlegm	57 (17)[c]	20 (8)	17 (4)
Cough and phlegm	27 (8)	10 (4)	13 (3)
Wheeze	33 (10)[d]	18 (7)	0 (0)
Any Symptom	77 (23)[e]	55 (22)	48 (11)

[a] Values are percent (number of subjects).
[b] $p < 0.07$ for current vs never.
[c] $p < 0.01$ for current vs quit and never.
[d] $p < 0.01$ for current vs never.
[e] $p < 0.059$ for current vs never.

The findings suggest that some respiratory symptoms in subjects with paraplegia are influenced significantly by cigarette use, whereas additional factors modulate symptoms in subjects with quadriplegia including, presumably, restrictive ventilatory impairment and airway hyperreactivity, as recently described. However, respiratory symptoms are unrelated to the completeness of motor injury.

Rectal Mechanics after Spinal Cord Injury: Comparison with Healthy Control. S. Mehta, S. Weinberger, W. A. Bauman, M. A. Korsten. Gastroenterology Section, Spinal and Injury Service and Spinal Cord Damage Research Center, and Bronx VA Medical Center, and Mount Sinai School of Medicine, New York, NY.

Patients with spinal cord injury (SCI) have significant problems with evacuation, nearly 20% complaining of intractable constipation. Previous studies using older technology demonstrated decreased rectal compliance and absent postprandial colonic motility and myoelectric activity. Using a highly compliant balloon barostat-manometry assembly (SVS/Barostat, Synectics Medical, Irving, TX), we studied six SCI patients and 6 healthy controls in the preprandial and postprandial state after a standard meal consisting of two cans of Two Cal HN (950 calories, protein 16.7%, fat 40.1%, carbohydrates 43.2%). After bowel cleansing and flexible sigmoidoscopy, patients were placed in the right lateral position. Colorectal compliance was studied at 3-minute intervals at seven different pressure levels (10, 13, 16, 19, 22, 25 mm Hg). Between each inflation, the balloon was deflated to the basal pressure of 7 mm Hg. The test meal was administered over a 10-minute period and the entire protocol repeated. Colonic pressures were simultaneously recorded using a low-compliance triple lumen, water-perfused polyvinyl system (Arndorfer pneumohydraulic infusion system).

Results: The two groups were matched in terms of age (58.5 vs 57.6 years) and all subjects were males. There was a significant difference in rectal compliance with the test meal between the patients (mean −20.50 mL) and the controls (mean 24.5 mL) (two-tailed t test, $p < 0.05$). This difference arose because of a *decrease* in rectal compliance with eating in healthy control as compared with a *increase* in patients with spinal cord injury. However, postprandial change in rectal compliance in each when calculated separately was not significant. Moreover, there was no change in the colonic motility between SCI and control groups. Finally, there was no difference in results when patients with complete versus incomplete injury were analyzed separately, although the groups were too small to draw any definite conclusions.

Conclusion: The decrease in compliance noted in healthy controls appears to be a neurally mediated spinal cord reflex initiated by the entry of food into the stomach. The abnormal postprandial colorectal response in patients with spinal cord damage may be implicated in the pathogenesis of constipation after SCI.

Absence of Lymphocyte Dysfunction in Spinal Cord Injury In an Identical Twins Study. C. B. Small, P. Lalezari, W. A. Bauman. Spinal Cord Damage Research Center, Bronx VA Medical Center, Division of Endocrinology, Department of Medicine, Mount Sinai School of Medicine, New York, NY; Divisions of Infectious Disease and Immunohematology, Department of Medicine, North Central Bronx Hospital, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, NY.

Respiratory, urinary tract, and skin infections pose a serious threat to the health of persons with spinal cord injury (SCI). Any factor predisposing these individuals to compromised ability to combat infection should be vigorously defined. Several theoretical etiologies may exist for potential immune dysfunction in those with SCI, including inadequate nutrition, reduced anabolic hormones (i.e., growth hormone or the sex steroids), psychological factors (i.e., stress or depression), as well as denervation of sympathetic outflow in those with injury above thoracic level six. Indeed, impaired T lymphocyte blastogenesis to the nonspecific mitogens concanavalin A, poke weed, and phytohemaglutinin has been described in five individuals with cervical injury. However, genetic variability in immune response is well appreciated. Controlling for genetic variability, we studied the lymphocyte subset populations and function in monozygotic twins, one of whom had a SCI (five with paraplegia and one with tetraplegia). The results are expressed as mean ± SEM. A paired t test was used to compare the groups.

Twins	T cell no.	CD4	CD8
SCI	75 ± 3.0	49.8 ± 3.4	23.0 ± 3.4
NonSCI	73 ± 3.8	49.8 ± 3.7	22.8 ± 1.9

NK Killer	CDC MC	Mitogen
25.7 ± 4.4	19.7 ± 3.3	55,458 ± 7,826
29.6 ± 4.2	14.9 ± 3.7	51,393 ± 7,376

No significant difference was found between SCI and nonSCI twins for any lymphocyte subset or function. As such, SCI *per se* does not appear to depress the immune response. According to prior studies, it is conceivable that level of lesion may play a role in immune dysfunction. To address this consideration, we plan on investigating sets of monozygotic twins with tetraplegia.

Arm and Leg Ergometry in Monozygotic Twins: One with Spinal Cord Injury. A. M. Spungen, Y.-G. Zhong, and W. A. Bauman. Spinal Cord Damage Research Center, Bronx VA Medical Center, Division of Endocrinology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Maximal arm ergometry exercise testing was performed in five pairs of identical twins, one of whom had a traumatic chronic spinal cord injury (SCI). Arm ergometry was performed to compare the SCI twins with the nonSCI twins, leg ergometry was performed to compared values of arm work with the more standardized leg work. Arm ergometry testing consisted of a 12 watt/minute incremental exercise protocol. Leg ergometry testing consisted of a 25 watt/minute ramp protocol. Maximal exercise criteria consisted of heart rate (HR) ≥85% of maximum predicted HR, leveling off of oxygen consumption (Vo_2) with continued increases in workload, and/or a respiratory exchange ratio (RER) of ≥1.10. Two separate paired t test comparisons were made: (1) SCI ARM vs nonSCI ARM and (2) nonSCI ARM vs nonSCI LEG. The results are reported as means ± SD.

	Preexercise			Anaerobic Threshold	
	SCI ARM	nonSCI ARM	nonSCI LEG	SCI ARM	nonSCI ARM
HR	90 ±14	84 ±12	93 ±10	153[a] ±12	121[b] ±6
VE	11.8 ±3.0	13.7 ±2.7	14.9 ±7.7	42.5 ±18.4	38.4 ±16.1
Vo_2	0.349 ±0.069	0.431 ±0.74	0.425 ±0.195	1.404 ±0.396	1.182[b] ±0.492
LA	1.1 ±0.4	1.0 ±0.4	1.2 ±0.3	4.4 ±1.1	4.1 ±0.9
WKLD	0	0	0	104 ±39	74[b] ±32

	Anaerobic Threshold	Peak Exercise			
	nonSCI LEG	SCI ARM	nonSCI ARM	nonSCI LEG	Predicted Maximum
HR	135 ±11	185 ±6	182 ±2	179 ±5	187 ±4
VE	41.6 ±13.3	89.8 ±40.7	100.2 ±29.9	105.9 ±38.7	146 ±28
Vo_2	1.478 ±0.415	2.138 ±0.726	2.103[b] ±0.494	2.540 ±0.770	2.888 ±0.454
LA	3.6 ±1.5	10.3 ±4.2	14.8[b] ±4.3	8.3 ±5.1	>4.0
WKLD	127 ±30	132 ±31	142[b] ±26	236 ±57	220 ±40

[a] $p < 0.01$ for SCI ARM vs nonSCI ARM.
[b] $p \leqslant 0.05$ for nonSCI ARM vs nonSCI LEG.
[c] HR, heart rate (bpm); VE, ventilation (L/min); Vo_2, oxygen consumption (L/min); LA, lactic acid (mmol/L); WKLD, workload (watts).

No significant differences were noted among the groups for the preexercise values. HR(AT) ($p < 0.01$) and Vo_2(AT) (N.S.) were higher in the SCI ARM than in the nonSCI ARM. HR(AT), Vo_2(AT), and WKLD(AT) were significantly lower in nonSCI ARM vs nonSCI LEG. ARM pkEX values were not significantly different between the twins. Vo_2(pkEX) and WKLD(pkEX) were significantly lower in nonSCI ARM vs nonSCI LEG. LA(pkEX) was significantly greater in the nonSCI ARM vs nonSCI.

The Effect of Spinal Cord Injury on Body Composition: an Identical Twin Study. A. M. Spungen, W. A. Bauman, J. Wang, and R. N. Pierson, Jr. Spinal Cord Damage Research Center, Bronx VA Medical Center, Division of Endocrinology, Department of Medicine, Mount Sinai School of Medicine, New York, NY; The Body Composition Unit, Columbia-St. Luke's/Roosevelt Hospital Center, New York NY.

Fat-free mass (FFM) is composed of the metabolically active tissues of muscle, viscera, and bone. FFM is a measurement of the quantity of lean tissue, whereas total body potassium (TBK) is a function of the quality of the lean tissue. The objective of this study is to determine the effect of spinal cord injury (SCI) on FFM and the concurrent reduction in resting energy expenditure (REE). The design consisted of a two group (SCI and NonSCI) matched sample. Five pairs of identical twins, one twin having SCI, were studied. The mean age and height of the total group was 37 ± 4 years and 1.8 ± 0.02 m. The mean weights for SCI and nonSCI were 70.0 ± 3.8 and 80.2 ± 6.5, $p < 0.05$, respectively. Duration of injury for the SCI group was 14 ± 5 years. Twin zygosity testing was performed in all pairs for DNA patterns at six loci (Lifecodes Corp, Stamford, CT). All five pairs were found to be consistent with monozygosity with a probability of being nonidentical of 1 in 4,096. FFM was analyzed by dual-photon x-ray absorptiometry (Lunar Model DPX, Madison, WI) and TBK (4-Pi counting chamber). Data were analyzed by a paired *t* test and simple regression. The results are reported as mean ± SE; $p < 0.05$.

	Soft Tissue			
	TBK (mEq)	FFM (kg)	Fat Mass (kg)	TBK/FFM (mEq/kg)
SCI twin	2800 ± 252	33.0 ± 6.7	15.5 ± 4.6	55.0 ± 4.1
NonSCI twin	417 ± 417	42.8 ± 6.8	16.8 ± 5.2	66.2 ± 4.4

In the twins with SCI, FFM and TBK were reduced compared with the nonSCI group. The ratio of TBK/FFM, a measure of the quality of lean tissue, was reduced in the SCI twins compared with the nonSCI twins. Fat mass was comparable in the two groups.

In conclusion, there was an 18% decrease in lean tissue in SCI twins compared with their co-twins.

Thyroid Hormone Levels in Chronic Spinal Cord Injury: An Identical Twin Study. Y.-G. Zhong and W. A. Bauman. Spinal Cord Damage Research Center, Bronx VA Medical Center, Division of Endocrinology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Any catastrophic illness or stress may depress the hypothalamic-pituitary-thyroid axis. In patients with acute or subacute spinal cord injury (SCI), thyroxin (T_4) levels have been reported to be low and triiodothyronine (T_3) depressed with elevated levels of reverse T_3, suggesting a reduction in 5′-deiodinase activity. A recent study of subjects with chronic SCI found significantly depressed T_3 and T_4 levels in subjects with SCI compared with controls. Genetic variability may influence thyroid hormone levels. Controlling for genetic variability, we studied serum levels of T_3, T_4, and thyroid-stimulating hormone (TSH) in nine sets of healthy monozygotic twins, one with a SCI (seven with paraplegia and two with tetraplegia). For each hormone determination, all samples were determined simultaneously in a radioimmunoassay (Abbott Diagnostics).

Results are expressed as mean ± SEM. Age of the twin pairs was 39 ± 2.2 years. Seven are male and two are female. SCI twins had a duration of injury of 14 ± 2.9 years. A paired *t* test was used for comparing the groups.

Twins	T_3 (ng/dL)	T_4 (μg/dL)	TSH (μIU/mL)
SCI	91 ± 4.7	7.9 ± 0.5*	1.2 ± 0.3
NonSCI	94 ± 6.9	7.1 ± 0.5	1.5 ± 0.5
Normal range	58–194	4.8–12.8	0.43–3.8

All values for thyroid function tests were in the normal range. However, there was a slight but significant increase in the T_4 level and no significant difference in T_3 level in the twins with SCI. In the absence of any significant difference in TSH concentration, this may be a consequence of a mildly altered pituitary response. However, levels of thyroid-binding globulin should be determined to exclude a subtle elevation in thyroid-binding protein. In contrast to previous reports, there was absolutely no evidence of depressed thyroid function, or low T_3 syndrome, in these healthy, genetically matched subjects with SCI.

Queens Medical Center

An Unusual Presentation of Advanced Ovarian Carcinoma in an Human Immunodeficiency Virus Positive Patient. M. Affifi, M. Reed, and I. Ashley. Mount Sinai Services at Queens Medical Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Persons who are infected with the human immunodeficiency virus (HIV) appear to have aggressive spread of genital and extragenital malignancies. We describe an unusual clinical course of a young HIV-seropositive woman who remains alive and well 28 months after resection of lung and ovarian neoplasms.

Case History: A 34-year-old black woman with a 22 pack year smoking history underwent a right lower lobe wedge resection of a malignant "coin lesion" in April 1993. The coin lesion had been noted on previous chest x-rays for more than 2 years before resection. Preoperative CD4 count was 1221. Six months after this resection she presented with progressive abdominal distension, ascites, and an enlarging pelvic mass. Subsequent evaluation revealed the presence of bilateral ovarian neoplasms. Preoperatively, CD4 count was 631 and serum CA-125 was 140 U/mL. The patient underwent exploratory laparotomy and total abdominal hysterectomy and bilateral salpingo-oopherectomy in November 1993. An infiltrating, poorly differentiated carcinoma with vascular and lymphatic invasion involving both ovaries was found on pathologic examination. The ovarian capsule, peritoneal washings, and all margins were negative for tumor. No additional therapy was given.

After comparing both lung and ovarian tumor histologies, our pathologists favored the ovarian tumor as primary. However, they could not exclude the alternative assessment that the previously resected lung adenocarcinoma metastasized to both ovaries. Either clinical scenario describes a highly unusual clinical course within or without the setting of HIV infection.

Conclusion: As patients with HIV infection survive longer, more extragenital and genital malignancies will continue to be seen among them. Higher CD4 levels may identify a favorable prognostic group. We suggest that unusual manifestations of metastatic tumors are more frequently encountered in the setting of HIV infection. Aggressive diagnostic and therapeutic surgical management may result in extended survival particularly when isolated metastatic sites are present in these patients.

Study of Sexual Dysfunction in Minority Patients with Breast Cancer. I. Ashley, M. Reed, and P. Agnelli. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Background: We undertook a pilot study to elucidate the sexual and psychological dysfunction of patients with breast cancer, most of whom are from minority populations. Few such studies on minority populations have been reported. The influence of pain management on sexual dysfunction was also analyzed.

Method: A specially formulated questionnaire was given to patients to retrospectively assess the impact of surgery, chemotherapy, radiation, and hormonal therapy on sexual function. A control group with benign breast disease at the same hospital was used for comparison.

Results: The 25 patients studied were Hispanics (24%), African Americans (40%), West Indians (32%), and East Indians (4%). Of these patients, 56% had medical insurance and 92% were unemployed; their mean age was 54 years. The patients were widowed, separated or single (56%), divorced (12%), or married (32%). At the time of diagnosis 72% were shocked, surprised, or devastated; 12% were depressed, 8% were unaffected, and 8% just accepted the diagnosis without reaction. After treatment, 68% had a desire for sexual intercourse, sexual pleasure, sexual fantasies, or orgasm, whereas 32% had no sexual desires.

Sexual Activity: Scale 1 to 10, with 1 = very infrequent and 10 = very frequent.

	1–3	3–6	7–10
Before diagnosis	44	40	16
After diagnosis	72	12	16
Self-image before diagnosis	0	12	88
Self-image after diagnosis	40	28	32

Values are given as percent.

The treatments that had an impacted on sexual function were chemotherapy (28%), surgery (24%), hormonal therapy (4%), radiation therapy/chemotherapy (8%), and chemotherapy/hormonal therapy (4%). Most patients (84%) felt that their pain was controlled with little or no effect on their sexual function.

The Control Group was similar in ethnicity, medical insurance, and marital status. They were depressed (75%) or shocked (25%) when told about their breast cancer. No changes were noted in sexual activity before and after the breast biopsy (that is, those who were sexually active remained active). Also, little if any modifications were noted in self-image before and after biopsy. They maintained their desire for sexual intercourse, pleasure, or fantasies (75%).

Discussion and Conclusion: Of the 25 patients who participated in the study, most (92%) are unemployed and many (44%) have no health insurance. The emotional response at the time of diagnosis was one of surprise, devastation, shock, or depression. The frequency of sexual activity decreased after the diagnosis of breast cancer. However, a large majority retained sexual desires. The treatments that had the greatest impact on sexual function were chemotherapy (28%) and surgery (24%). The patient's self-image decreased after the diagnosis of breast cancer. Eighty-four percent felt that their pain was controlled with little impact on their sexual activity. An overwhelming majority (80%) thought that a support group would be helpful.

Sweat Gland Carcinoma (Malignant Nodular Hidradenoma): Case Report and Review of the Literature. I. Ashley, M. Reed, and A. Chernys. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Background: We report about a 57-year-old Hispanic man with malignant nodular hidradenoma. The patient had three biopsy-proven recurrent benign nodular hidradenomas across the left cheek over a 2-year period. A fourth recurrent lesion several months later had malignant histology. Malignant transformation of this usually benign tumor is very rare. Little is known about this rare tumor and treatment modalities. Recommendations for wide surgical excision and, in some cases, local radiation or systemic chemotherapy are based on anecdotal cases.

Method: We reviewed 89 cases published in the literature and analyzed and compiled the data to elucidate the nature of this tumor and best treatment course.

Results: The typical history is that of a long-standing cutaneous nodule that begins to enlarge rapidly with or without ulceration or color changes. Histologically, the lesions vary from undifferentiated areas to carcinoma with squamous and glandular differentiation. The natural course of this neoplasm varies. Some patients are cured by surgery, others develop lymph node metastases, whereas some die from diffuse metastatic disease. The pathological diagnosis is established by Hematoxylin-Eosin staining. The mean age at diagnosis is 57.5 years with equal male to female distribution. The tumor distribution is as follows: lower extremities, 30%; upper extremities, 25%; trunk, 17%; head, 23%; neck, 3%. Metastatic sites: lymph nodes, 16.8%; bone, 3.3%; viscera, 3.3%; lung/pleura, 4.4%. Malignant sweat gland neoplasms have a propensity for local and regional lymph node recurrence (as high as 54%). Prognostic features depend on histology, grade, and metastatic sites. The potential benefit of lymph node dissection is unclear. Anecdotal reports suggest that clinically involved and uninvolved nodal drainage should be excised and irradiated. However, the role of adjuvant radiotherapy is not yet well defined. Features such as dermal lymphatic invasion, nerve-sheath involvement, deep structure infiltration, margins of resection positive for tumor, highly anaplastic morphology, and extracapsular lymph node extension may help identify high risk for recurrence and encourage consideration of postexcisional radiotherapy. The role of chemotherapy is presently undefined.

Conclusion: Treatment decisions need to be formalized by conducing a well-structured clinical trial.

Transient T_3 Antibodies Unassociated with Thyroglobulin Antibodies. A. Bishnoi, G. C. Schussler, and I. Sachmechi. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY, and SUNY Health Science Center, Brooklyn, NY.

Introduction: Antithyroid hormone antibodies have been described in various thyroidal and some autoimmune nonthyroidal disorders. Because thyroid hormones themselves are not immunogenic, thyroglobulin has been proposed as being the antigen responsible for production of these antibodies, leading to a high association between the two. We describe here a patient with transient anti-T_3 antibodies, in the absence of thyroid and nonthyroid autoimmune disease who had negative antithyroglobulin antibodies as determined by radioimmunoassay.

Case History: A 64-year-old man, during evaluation of thyroid function for nonspecific complaints, was found to have serum T_3 concentrations in the 664 to 880 ng/dL range without clinical evidence of thyrotoxicosis or other thyroid disease. T_4 was normal and thryrotropin, although temporarily suppressed by solumedrol treatment for chronic obstructive pulmonary disease, became normal when discontinued. Serum-free T_3 by equilibrium dialysis was normal; so were antithyroglobulin and antiperoxidase antibodies as determined by radioimmunoassay.

Method: Antithyroid hormone antibodies were detected by incubating ^{125}I-triiodothyroxine and I^{131}-thyroxine with patients' serum at 4°C for 16 hours, after which 200 μL of γ-globulin was added as a carrier. The γ-globulin was then precipitated with 25% polyethylene glycol. Polyethylene glycol selectively precipitated T_3 from serum incubated with radioactively labeled T_3 and T_4. The tracer T_3 could be displaced from the precipitable antibody by T_3 but not by T_4 or T_4 analogs. Antibodies to T_3 persisted for 5 months after which they disappeared; the T_3 radioimmunoassay also reverted to normal.

Summary: The absence of antithyroglobulin antibodies in the presence of anti-T_4 or T_3 antibodies has been attributed to the insensitive hemagglutination method of detection. In the present case, antithyroglobulin antibodies were absent on testing with the more sensitive radioimmunoassay method. We propose that T_3 cross-reacted with an antibody against a nonthyroid immunogen.

"Beer Potomania" in a Non-Beer Drinker. D. A. Blaustein and P. Das. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Beer potomania is a disease characterized by recent binging with beer (which is poor in salt) in association with a minimal intake of ordinary food. Lack of dietary proteins decreases urea production. Insufficient delivery of salt and urea may alter the ability of the kidney to adjust medullary solute concentration and consequently the urine. Failure to dilute the urine maximally limits the ability to excrete free water and water intoxication (hyponatremia, hypokalemia, hypochloremia, etc.) may become evident. The clinical examination is consistent with euvolemia.

Case Report: A 42-year-old woman was admitted to the hospital for evaluation of new-onset generalized seizures (two episodes on the day of admission). She had a history of alcohol abuse in the form of several binging episodes in the past. This time she had been drinking for the past 10 days, 1 to 2 pints of wine and vodka along with about 2 to 3 L of water a day. She stated that she was not thirsty but that she was trying "to flush the alcohol with water." She consumed minimal food during this period and denied taking medications. The physical examination was significant only for agitation and malnutrition (weight = 110 pounds; height = 5 feet, 4 inches). Laboratory results showed: *Na = 114 mEq/L;* K = 3.26 mEq/L; CO_2 = 22 mEq/L; Cl = 74 mEq/L; blood urea nitrogen = 4 mg/dL; creatinine = 0.5 mg/dL. The blood alcohol level was 210 mg/dL. Urine electrolytes: Na = 10 mEq/L; K = 10 mEq/L; *urine osmolality = 75 mosm/L*. The results of a brain computed tomography scan were normal. Hyponatremia was thought to be cause of the patient's neurologic symptoms. She received 150 cc of 3% saline during the first 5 hours along with 30 mEq of potassium chloride. During the rest of the first 24 hours she was given 2.5 L of 0.9% saline and 1.6 L of oral fluids. She had a urine output of 8.4 L during the same period. Her mental status improved rapidly and the electrolytes normalized during the next 24 hours. Follow-up levels on alcohol and osmolalities were not sent. She had no further episodes of seizures during the rest of her hospital stay.

Conclusions: We describe a case of symptomatic hyponatremia which resembles beer potomania, but that was secondary to the intake of vodka, wine, and water. The fact that this patient became hyponatremic with an intake of only 3 to 4 L a day of fluids, along with an appropriately low urine osmolality might possibly be explained by a mechanism similar to the one responsible for beer potomania. Previous reports of hyponatremia secondary to ingestion of similar amounts of alcohol and water were associated with higher values of urine osmolality. Whether antidiuretic hormone secretion was not turned off or its metabolism was impaired, or both, has not been elucidated. To the best of our knowledge, this is the first report of "beer potomania" in a nonbeer drinker.

Cyclophosphamide Treatment of Lupus Nephritis. D. A. Blaustein, R. Faiyaz, and A. Opran. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Diffuse proliferative glomerulonephritis (DPGN) is the most common and aggressive type of lupus nephritis. Treatment of DPGN consists of six monthly intravenous pulses of cyclophosphamide. In recent studies this treatment is followed by a quarterly maintenance regimen for 2 years. In patients with relatively preserved renal function, renal survival is significantly enhanced by the addition of cyclophosphamide. Data are less encouraging in patients with severely depressed renal function.

Study Design: We performed a retrospective study of patients with DPGN treated at Queens Hospital Center during the past 5 years. We obtained data from six patients (two with severe renal failure) who had follow-ups extending up to 4 years after initiation of therapy with cyclophosphamide.

Results: The response of DPGN to treatment varied according to the degree of renal function. Patients with early DPGN (relatively preserved renal function) had excellent responses to cyclophosphamide (Cases 1 to 4). In advanced DPGN (compromised renal function) the response to treatment was greatly diminished (Cases 5 and 6).

Conclusions: Patients with DPGN should be treated aggressively with cyclophosphamide. If renal function is relatively preserved, the response to treatment is excellent. If renal function is compromised, the response to treatment is diminished and the incidence of side effects is increased. If no significant initial response is observed, it might be unwise to subject these patients to repeated courses of cyclophosphamide.

Parkinsonian Tremor Simulating Ventricular Tachycardia. S. Chockalingam, J. Walters, M. Sharma, and M. Raza. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Background: Ventricular tachycardia is a potentially lethal arrhythmia which may degenerate into ventricular fibrillation and result in sudden death. Ventricular tachycardia has to be differentiated from supraventricular tachycardia with aberrant conduction. Electrocardiographic artifacts are a frequent source of error in the diagnosis of arrhythmia. Parkinsonian tremor can be mistaken for atrial flutter. However, there are no reports of Parkinsonian tremor mimicking ventricular tachycardia.

Case Report: An 88-year-old Greek woman was admitted to the telemetry unit with a history of dizzy spells. The resting electrocardiogram showed normal sinus rhythm with frequent premature atrial contractions and nonspecific ST and T wave charges. While the patient was being monitored, the alarm went off. The rhythm appeared to be ventricular tachycardia. The intern on duty examined the patient, who was alert with normal blood pressure. The pulse was 60 bpm and regular; however, the monitor showed ventricular tachycardia. The patient was found to have coarse Parkinsonian tremor; as the tremor became less coarse the rhythm mimicked atrial flutter with 5:1 A-V conduction. When the tremor ceased, the patient was found to have normal sinus rhythm on the monitor. On several occasions a similar rhythm was observed on the monitor while she had tremors, and the rhythm changed when the tremor ceased.

Conclusion: This case illustrates that Parkinsonian tremor can simulate both atrial flutter and ventricular tachycardia. However, a careful examination at the bedside can prevent diagnostic misadventure.

Investigation of Purified Protein Derivative Conversion Rates in Health Care Workers in a Municipal Hospital. B. T. Edwards, C. Stokes, B. Mills, and D. J. Brennessel. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Reported nationwide rates of annual purified protein derivative (PPD) conversion in health care workers (HCW) are <2%. The annual rates among employees at Queens Hospital Center, a municipal hospital in Queens, NY, were 5.0% in 1993 and 4.9% in 1994.

Method: A retrospective investigation was done to identify risk factors including work area, job description, and known exposure to an infectious patient during 1993 and 1994.

Results: A high prevalence of positive tuberculin skin tests in new employees (191/810, 24% total) was noted, suggesting a high prevalence of tuberculosis in the community. Among current employees, 39 (41%) of 95 PPD converters worked in low-risk areas as defined by Centers for Disease Control guidelines (see Table).

TABLE.
PPD Conversions 1993–1994

	No.	% of Total
Low risk	39	41
Intermediate risk	22	23
High risk	34	36
Total	95	100

Only 12 of 95 converters had known exposure to infectious patients. **Conclusion:** Interpretation of PPD conversion rates in HCWs should include risk assessment based on the prevalence of positive PPDs in the community as well as the work area or occupation group.

Bronchiolitis Obliterans Organizing Pneumonia in Systemic Lupus Erythematosus. S. Kaul, J. K. Fleischman, V. Azueta, and A. Opran. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Background: Bronchiolitis obliterans organizing pneumonia (BOOP) is a distinct clinicopathologic entity characterized by cough, fever, and progressive dyspnea; patchy infiltrates on chest roentgenogram; and a histologic pattern of intraluminal organization predominantly within alveolar ducts. It has been described in association with several connective tissue diseases such as rheumatoid arthritis, polymyositis-dermatomyositis, and mixed connective tissue disease. Reports of BOOP in patients with systemic lupus erythematosus (SLE) are rare. We report a patient with SLE who presented with a subacute respiratory illness and an unusual radiographic appearance of multiple pulmonary nodules caused by BOOP.

Case Report: A 41-year-old nonsmoking black woman with a 10-year history of SLE was admitted for evaluation of fever, persistent cough, mild dyspnea, and a left foot drop. She denied being a smoker. Medications included prednisone (20 mg/day) and ranitidine. Physical examination was remarkable for a temperature of 101.5°F and a left foot drop. Chest roentgenogram demonstrated bilateral upper lobe nodular infiltrates. Computed tomographic scan of the chest showed multiple bilateral nodular parenchymal infiltrates in the upper lobes and superior segment of the left lower lobe without mediastinal adenopathy. Bronchoscopy with bronchoalveolar lavage was inconclusive. Patient refused an open lung biopsy. A left superficial peroneal nerve biopsy revealed severe chronic axonopathy with active degeneration. Vessels in the epineurium showed vasculitis. Because of the documented vasculitis, prednisone was increased from 20 to 60 mg/day. Patient's persistent cough, fever, and radiographic abnormalities improved significantly on this therapy. Prednisone was tapered over an 8-week period to 20 mg/day as an out-patient. A few weeks after the prednisone was tapered, she returned with recurrence of cough, fever, arthralgia, and two enlarging right upper lobe nodules. An open lung biopsy was performed at this time and revealed BOOP.

Discussion: BOOP is an interstitial lung disease with a clinical onset that is often acute and mimics an atypical pneumonia. The characteristic radiographic appearance of BOOP is bilateral patchy alveolar opacities. Pathologically it is characterized by the presence of granulation tissue plugs within the lumen of bronchioles and alveolar ducts together with patchy areas of organizing pneumonia. The connective tissue disorders BOOP has been associated with include rheumatoid arthritis, dermatomyositis-polymyositis, and mixed connective tissue disease. To our knowledge, our case is the first report of SLE-related BOOP presenting as multiple nodular infiltrates.

Presentation of Early Lesions of Colorectal Adenocarcinoma at a Municipal Hospital in New York City.

T. Linden, M. E. Hirth, E. Ahmed, R. Haque-Salam, and Y. Twersky. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Background: Survival of patients with colorectal adenocarcinoma correlates with the stage of disease at the time of diagnosis. Detection of early lesions can markedly reduce mortality. To facilitate such early detection, we determined the presentation of colorectal adenocarcinoma in 100 consecutive patients at a municipal hospital in New York City.

Methods: Tumor registry records and hospital charts from 100 consecutive colorectal adenocarcinomas were evaluated retrospectively. Data were compiled based on sex, site (distal vs proximal to the splenic flexure), stage (early [CIS + I], intermediate [II] and late [III + IV], and presenting symptom.

Results: There were 42 men and 58 women. Two (5%) men and 16 (28%) women were found by routine screening using fecal occult blood tests (FOBT) or flexible sigmoidoscopy (FS). This difference may account for the variance in stage such that 7 (16%) men and 21 (36%) women presented with early-stage lesions. The National Cancer Data Base (NCDB) reported a gradual shift toward more proximal cancer with 53% proximal, 41% distal, and 5% unspecified in 1990. By contrast, in our patients there were 29% proximal, 68% distal, and 3% unspecified. Distal lesions were more likely to be early stage than proximal lesions (23/68 [34%] vs 4/29 [14%]). The most common presentation of distal lesions was rectal bleeding (43%), followed by pain or obstruction (28%), and 13% were detected by routine screening (FOBT or FS). The four cancers found by FS were all early stage. FOBT detected 13 cancers, 8 of these (62%) were proximal. Of these 13 cancers, 5 (38%) were early stage. Of the 75 lesions detected clinically, 19 (25%) were early stage. These patients' presentation included bleeding (13/34), weight loss (2/3), pain/obstruction (2/29), constipation/diarrhea (1/4), anemia (1/5).

Conclusions: Significant differences were noted between the NCDB and our population. In our patients 29% of the cancers were proximal and 68% were distal versus 53% and 41%, respectively, in the NCDB. This trend toward distal lesions may be explained by several factors which include the large segment of recent immigrants in our population who may not have been screened before the index presentation. All the cancers found by screening FS and 38% of the cancers detected by FOBT were early stage. Further, because 62% of the cancers detected by FOBT were proximal, this modality complemented FS in screening for colon cancer. The majority of cancers diagnosed at an early stage were detected by methods readily available to primary care physicians. Clinical clues should be aggressively pursued as 25% of the cancers detected on clinical grounds were early stage.

Parvovirus Infection in an Otherwise Healthy Young Woman.

J. Malakar, B. Edwards, and C. Feiner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Departments of Medicine and Geriatrics, Mount Sinai School of Medicine, New York, NY.

Introduction: We report a case of parvovirus infection in an otherwise healthy young woman who required hospitalization because of a decline in functional status.

Case Report: A 23-year-old white female student complained of a rash on her upper abdomen and lower extremities which she attributed to sun exposure during an outdoor concert. The rash gradually cleared but recurred 5 days later associated with severe prostration, fatigue, and joint pain. Her temperature was 99.7°F. She had a diffuse punctate erythematous rash most prominent over the upper and lower extremities. Over 2 days, the joint pain progressed to the point that she needed assistance for ambulation. She had positive serum IgG and IgM parvovirus titers. The patient's symptoms resolved within several days.

Conclusion: Parvovirus infection is not a diagnosis limited to a pediatric age group; it should be suspected in adults who present with fever, rash, and arthralgias.

Coronary Artery Ostial Stenosis Secondary to Radiation Therapy.

A. Pulijaal, J. Postman, H. Soto, T. Cooke, and M. Raza. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Background: Cardiac sequelae to mediastinal radiation have been recognized during the past three decades. Although postradiation therapy (RT) lesions of coronary vessels have been considered rare, it now is generally known that these can present as acute and chronic pericarditis, cardiomyopathy from myocardial fibrosis, regurgitant valvular lesions, and conduction system impairment, usually as third degree A-V block. Analysis of current data indicates a small but significant incidence of coronary artery disease following RT using doses of radiation greater than 4000 rad without cardiac shielding and delivered anteriorly. Ostial and proximal stenosis is a hallmark of coronary artery disease following radiation. However ostial stenosis of the left main coronary artery (LMCA) is rare. Only five cases have been described in the literature. It was suspected in an additional patient who died suddenly after injection of contrast material into the aortic root.

Case Report: A 41-year old African-American woman presented to Queens Hospital Center with a complaint of feeling dizzy, near syncope. Her third degree A-V block responded to intravenous atropine. The electrocardiographic pattern was that of inferior wall ischemia. Additionally, enzyme studies suggested acute myocardial infarction. Her only risk factors for coronary artery disease were chronic smoking and exposure to mantle radiation 25 years ago for the treatment of Hodgkins' disease. She had a hemodynamically insignificant ejection systolic murmur in the pulmonic area with normal cardiovascular examination. Her complete blood cell count and blood chemistries (SMA 18), and lipid profiles were normal. The patient underwent cardiac catheterization which revealed significant ostial stenosis of the right and the left main coronary arteries. During catheterization the patient was noted to have acute ST elevations in inferior leads without any chest pain but with hypotension requiring hemodynamic stabilization with intraaortic balloon pumping. She underwent emergency coronary bypass surgery with grafts to left anterior descendens, left circumflex, and right coronary artery. Intraoperatively, no other significant lesions were found besides the ostial lesions. The subsequent postoperative course was uneventful.

Conclusion: Coronary ostial stenosis is a rare condition with diverse etiologies such as Takayasu's disease, syphilitic aortitis, congenital coronary abnormalities, iatrogenic coronary ostial stenosis secondary to cardiac catheterization, or surgery. Only a few cases of ostial stenosis have been reported in premenopausal women. We believe that the patient's LMCA and right coronary ostial stenosis were caused by radiation therapy which had been administered 25 years previously.

Leukemic Phase True Histiocytic Lymphoma and Monocytic Leukemia: Semantic Debate versus Distinct Clinical Entities. M. Reed, I. Ashley, and A. Thomas. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: We describe a case of monocytic leukemia which was initially diagnosed as an aggressive non-Hodgkin's lymphoma of true histiocytic origin (THL). Because the initial treatment may differ for these malignancies, the debate about their classification remains an important one.

Case Report: A 30-year-old human immunodeficiency virus (HIV)-negative asymptomatic black man presented with progressive lymphadenopathy in the cervical and supraclavicular regions bilaterally. Cervical lymph node biopsy in December 1993 revealed intermediate grade diffuse small cleaved lymphoma. A staging workup revealed Stage IV disease, consisting of bilateral cervical and supraclavicular adenopathy and bone marrow tumor involvement. Before initiation of therapy the patient developed marked weakness, fever, shortness of breath, rapid weight loss, night sweats, leukopenia, and marked anemia. Repeat bone marrow biopsy was done and showed replacement with "lymphoid-type" tumor cells and areas of phagocytosis of erythroid cells. After antibiotics were given to control infection, the patient was started on combination chemotherapy. He achieved a short-lived hematologic remission after three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Computed tomographic scan of the neck before and after therapy confirmed marked resolution of bulky adenopathy. Eight weeks after receiving two additional cycles of anti-leukemia type consolidation regimens, the patient developed abdominal pain and was found to have bulky abdominal disease and return of extensive marrow infiltration. He had a progressive downhill course and died after an episode of intracranial hemorrhage 8 months after diagnosis.

Immunophenotyping of the cervical and bone marrow specimens were performed. The lymph node was negative for all B and T cell markers but was positive for CD43. Two parameter FAC scans using several T, B, myeloid, and monocytic markers were performed on lysed bone marrow cells and showed that the tumor cells were of monocytic lineage. Bone marrow karyotyping revealed a deletion of the long arm of chromosome 11 (q23), and a translocation between chromosomes 1 and 3. These karyotype abnormalities are more consistent with acute myelogenous leukemia (AML) than lymphoma.

Conclusion: Many of the reports of true histiocytic lymphomas (THL) in the literature describe cases with bone marrow involvement. The similarities that exist between the rarely encountered THL, representing 1% of all non-Hodgkin's lymphomas, and the infrequently seen (M5b) monocytic leukemia, representing 5% of AML cases, have also been well described in recent reports. We conclude, as suggested by Ralkiaer et al., that these entities represent a common spectrum of monocytic malignancies. Our patient's clinical course, although containing some atypical features such as low white blood cell count and absent CD34 on all bone marrow immunophenotyping, had a karyotypic picture most consistent with M5b acute monocytic leukemia.

Rapid Reversal of Ifosfamide Neurotoxicity with Methylene Blue. M. Reed, A. Thomas, and R. Balmiki. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: We present a patient with an unusual tumor with a variant course who developed neurotoxicity to ifosfamide and responded to methylene blue administration.

Case Report: A 52-year-old woman with a cystic ovarian teratoma containing a squamous cell carcinomatous component underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy in 1984. Recurrent deep venous thrombosis in 1991 was associated with recurrent squamous cell carcinoma involving inguinal lymph nodes. The patient received 5-fluorouracil, mitomycin, and radiotherapy followed by five cycles of carboplatinum and 5-fluorouracil with complete resolution of symptoms and masses. In February 1993 no abnormal masses or inguinal adenopathy were seen on computed tomography (CT) scan. In July 1994 the patient's abdominal pain and tumor recurred. The patient was again treated with 5-fluorouracil and carboplatinum followed by taxol, but without response. Single agent ifosfamide, 3 g/m^2, was then administered along with mesna, a prophylactic agent which was used to prevent hemorrhagic cystitis induced by acrolein, the urotoxic metabolite of ifosfamide. On the third day of ifosfamide therapy the patient had a marked change in mental status. She was found staring straight ahead with jerky movements of her right lower extremity, responding only to pain. A neurologist attributed the problem to metoclopramide and morphine, both of which were discontinued. Additional diphenhydramine was promptly given without any improvement. CT scan of the head and lumbar puncture results were normal. Ifosfamide neurotoxicity was suspected. Although ifosfamide was stopped at the onset of the neurological symptoms, non improvement was seen for more than 48 hours after discontinuation. However, her mental status notably improved within 35 to 40 minutes after the intravenous administration of 50 mg of methylene blue in saline. After four more doses of methylene blue every 6 hours, her neurological status returned to and remained normal. A spot urine glutaric acid was 248 μmol/L (normal range, 39–330 μm/L).

Discussion: Acute encephalopathy from ifosfamide is not rare and its mechanism remains unknown. The reported incidence ranges from 5 to 33%. Ifosfamide is often administered with other agents which may have an adverse impact on neurological function. Although encephalopathy caused by ifosfamide is usually reversible, it may cause death. Rapid reversal of ifosfamide-induced neurotoxicity has been reported with methylene blue. Our patient responded rapidly to this agent. Tumor response was not achieved. After discharge, the patient refused further chemotherapy. Several weeks later, she developed obstructive uropathy, sepsis, leukocytosis, and died. The sepsis did not occur in the neutropenic period.

Conclusion: A trial of methylene blue should be considered in the treatment of patients who develop acute encepholopathy after ifosfamide.

An Aggressive Follicular Carcinoma of the Thyroid with Unusual Metastases. L. Sachmechi, A. Bishnoi, R. N. Bitton, M. Patel, H. Parnes, M. Sharafatkhah, and S. Sanelli. Divisions of Endocrinology and Metabolism, Radiology and Neurology. Mount Sinai Services at the Queens Hospital Center, Jamaica, NY and the Long Island Jewish Medical Center, New Hyde Park, NY.

Introduction: We describe a patient with follicular thyroid cancer who presented with metastasis to the sphenoid sinus, a very rare occurrence.

Case Report: A 44-year-old Hispanic woman presented with a small (10 × 12 cm) cuboidal follicular cancer of the thyroid. Total thyroidectomy was followed by I^{131}-thyroid ablation. The patient was then lost to follow-up for 6 months. During that time she took no thyroid hormone. Total body scans (I^{131}) done 1, 3, and 5 years after surgery were negative. (Thyrotropin (TSH) $>$ 30 MIU/mL and thyroglobulin levels $<$5 μg/L on each occasion). Five and one half years after surgery, the patient developed cord compression secondary to thyroid metastases. This was treated with laminectomy and external radiation. Two years later, she complained of headaches and double vision. Magnetic resonance imaging revealed a soft tissue mass in the sphenoid sinus with destruction of the basisphenoid, clivus and floor of the sella, displacing the pituitary gland out of the sella turcica. Bone scan revealed focal abnormalities in the upper thoracic spine, ethmoid bones, and base of the skull. Biopsy showed thyroid follicular carcinoma. Pituitary testing revealed secondary hypoadrenalism. TSH was 0.01 MIU/μL and thyroglobulin was 20 μg/L.

Discussion: Metastases to the sinonasal tract are extremely rare. The thyroid is the primary tumor in only 3.8% of reported cases. In our patient, the tumor may have metastasized to the bone and then ruptured into the sphenoid sinus. The unusual features of this case are the marked aggressiveness of the tumor; perhaps promoted by a long period of hypothyroidism (caused by patient noncompliance with medications), and the failure of known tumor markers, i.e., serum thyroglobulin and total body scan, to identify these metastases in a subclinical state. Additional tumor markers are needed to detect disease in these patients.

The Role of the CD4:CD8 Ratio in Predicting Human Immunodeficiency Virus Coinfection in Patients with Newly Diagnosed Tuberculosis. R. A. Salazar, V. L. Souza, A. Khan, and J. K. Fleischman. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Purpose: Because of the clinical implications of human immunodeficiency virus (HIV) status on the duration of treatment for tuberculosis (TB), and in view of the low percentage of patients in whom HIV testing is performed, we evaluated immunologic function of patients with newly diagnosed TB and its ability to predict HIV coinfection.

Methods: Charts of patients with newly diagnosed TB and unknown HIV status from 1992 to 1995 at Queens Hospital Center were reviewed. Because of the known effects of TB treatment on CD4+ T-lymphocytes and in view of a lag in HIV seroconversion, we only included patients with T cell studies done within the first 2 weeks of treatment and HIV testing done within the first month of diagnosis. Patients with other acquired immunodeficiency deficiency syndrome (AIDS)-defining illnesses were excluded. Results were subjected to statistical analysis using *t* test for patients with different variances.

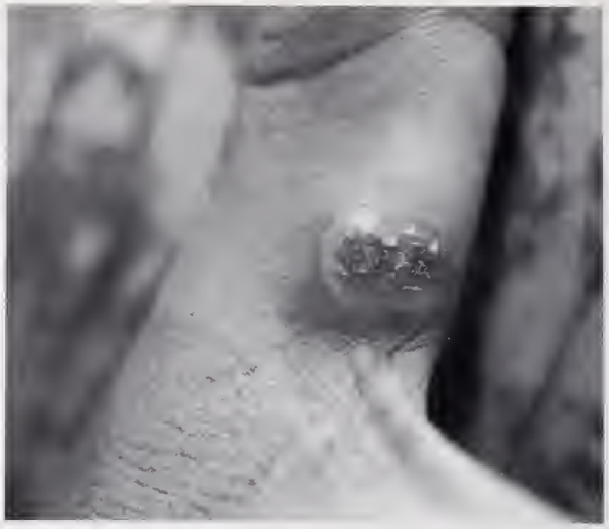
Results: Fifty-four patients were evaluated; 22 were HIV positive and 32 were HIV negative. There were no differences between groups with regard to age, sex, or race. There was no significant difference in the total T-lymphocytes between the two groups, but there were significant differences in the CD4, CD8, and CD4:CD8 ratios ($p = 0.05$).

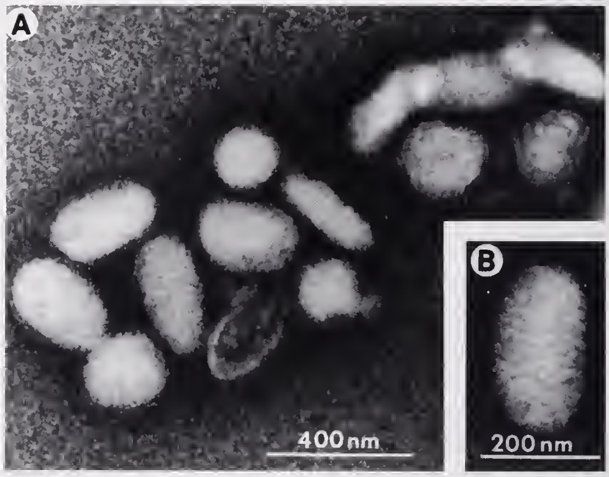
	HIV			
	Positive		Negative	
	Range	Mean	Range	Mean
Total T cell	90–2552	854	86–2438	1100
CD4	6–582	131	29–1488	641
CD8	89–3089	748	33–831	339
CD4:CD8	0.01–0.79	0.21	0.6–8.25	2.43

A CD:CD8 ratio of less than 0.8 gave a sensitivity of 100%, a specificity of 91%, positive predictive value of 88%, and a negative predictive value of 100% in predicting HIV coinfection.

Conclusion: HIV coinfection in patients with TB can be predicted on the basis of the CD4:CD8 ratio. In patients with newly diagnosed TB and unknown HIV status, the CD4:CD8 ratio can not only predict HIV coinfection but may be useful in determining length of treatment, particularly when HIV testing is refused.

Human Orf: Farmyard Pox in an Urban Setting. N. Varatharajah and D. J. Brennessel. Mount Sinai Services at Queens Hospital Center, Jamaica, NY; the Mount Sinai School of Medicine, New York, NY; and N. Chatterjee and W. Samsonoff, New York State Department of Health, Albany, NY.





Introduction: Orf is an uncommonly recognized zoonosis caused by a parapox virus found in goats and sheep and often present as a solitary skin nodule in humans. We report a case of Orf in an urban resident which is as complicated by erythema multiforme.

Case Report: A 32-year-old healthy man presented to a New York City hospital with a nodule on the base of his right thumb. Seven days previously, he had sustained an accidental abrasion of his thumb by the tooth of a goat on a farm on Long Island from which fresh goat meat is marketed. A small papule first appeared, which enlarged to a 2 × 1.2 cm ulcerated nodule (Fig. 1). There was no associated fever, chills, lymphadenitis, or adenopathy. Gram stain of the aspirated material revealed no leucocytes but Gram-positive cocci were seen. Culture grew *Staphylococcus epidermidis* and *Enterococcus faecalis* thought to be wound contaminants. Acid-fast smear was negative. Aspirate was sent to the New York State Department of Health Laboratory which confirmed the presence of Orf virus by electron microscopy (Fig. 2). Although the lesion healed progressively, the patient developed a mild erythema multiforme eruption 21 days after the nodule appeared.

Discussion: Orf is a relatively common zoonosis but rarely recognized and diagnosed in an urban setting. The characteristic skin lesion and history of contact with farm animals should be suggestive of Orf. The diagnosis of Orf can be confirmed by the electron microscopic demonstration of the characteristic virions which are ovoid, approximately 150 nm wide and 200 to 300 nm in length, and have a whorled surface filament pattern. Misdiagnosis may lead to unnecessary manipulation and surgery in this otherwise benign self-limited condition. Erythema multiforme, although nonspecific, is a condition known to be associated with Orf.

Information for Authors

THE MOUNT SINAI JOURNAL OF MEDICINE, established in 1934 as *The Journal of the Mount Sinai Hospital,* is a peer-reviewed general medical journal. It is indexed or abstracted in *Index Medicus, Current Contents, Science Citation Index, Hospital Literature Index, International Nursing Index, Excerpta Medica, Chemical Abstracts, Biological Abstracts,* and major databases. Theoretical and basic science articles for the clinician, reviews, reports of clinical or research experience, articles on any subject affecting the practice of medicine, short notes in any specialty, book reviews, letters, and articles by medical students are welcome. The *Journal* is a participant in the Agreement on Uniform Requirements for Manuscripts Submitted to Biomedical Journals. The *Journal* aims at responding to authors of manuscripts within 8 weeks of submission.

Communications. Address correspondence on manuscripts to: Editor, *The Mount Sinai Journal of Medicine,* The Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Phone: (212) 241-6108; FAX: (212) 722-6386; e-mail: msjournal@msvax.mssm.edu.

Authorship Responsibility, Financial Disclosure, and Assignment of Copyright. Each author is required to sign (1) the statement on authorship responsibility; (2) the statement on financial disclosure; and (3) either the statement on copyright transfer or the statement indicating that the author is or was a US government federal employee when this work was conducted and prepared for publication. These statements are printed from time to time on a page in the *Journal* entitled "Required Form for Authors" and can be photocopied for use. Copies may also be obtained from the *Journal* office. Use additional copies of the form if there are more than six authors, and replace with the appropriate number of the author, e.g., 7th, 8th, etc. The signed original form(s) should be submitted with the manuscript.

Manuscript Preparation. Submit manuscripts in triplicate, including three sets of illustrations (see below). **Manuscripts must be typewritten or computer generated, double spaced throughout (including references, legends, and tables),** on one side of 8½ × 11 inch white bond paper with generous margins. All pages except the title page should be numbered consecutively. Begin a new page for the title page, abstract, initial page of text, references, each table, and legends. A floppy disk, if available, should accompany the manuscript. The label on the disk should specify the name of the first author, the title of the manuscript, how the disk has been formatted, and the word processing system used (DOS, Windows, or Windows 95). PC format is preferred but a high-density formatted Macdisk is acceptable. The text should be in ASCII, Microsoft Word or Wordperfect. Other than the title page, the abstract page and each page of text should be numbered sequentially, and include a heading (top right) which identifies the last name of the first author.

Drugs must be identified by their generic names. Do not use abbreviations on the title or abstract page. Define all abbreviations on first use in the body of the manuscript.

Any material taken directly from other sources must be accompanied by a written statement from both the author and publisher giving permission to the *Journal* for reproducing it. The authors must document in the manuscript that all clinical investigations described in the manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board or its equivalent. The text must indicate that the informed consent of each subject was obtained. If results of experiments on animals are reported in the manuscript, the text must indicate that these studies were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office or its equivalent which supervises such work.

Title Page. The title page should be double spaced, and not numbered. It should indicate (1) title of the article, phrased as concisely as possible; (2) last and first name of each author, middle initials, if any, and not more than two academic degree(s); (3) institutional affiliation and title or rank of each author; (4) name and address of department(s) and institution(s) from which the work originated; (5) the name and address (and FAX number if available) of the author who will receive and respond to correspondence; (6) the name and full postal address of the author from whom reprint(s) are to be requested; (7) acknowledgments of sources of grant support; (8) name, place, and date of any conferences at which some or all of the information was presented; and, (9) a running head of fewer than 40 letter spaces. At the bottom of the title page, *list 3 to 10 key words or phrases* to facilitate indexing in accord with Medical Subject Headings from Index Medicus.

Abstract. All articles must include an abstract of not more than 250 words on the first numbered page of the manuscript. Abstracts should be double spaced and divided into four paragraphs:

Background: what problem(s) was(were) addressed;
Methods: how the study was performed;
Results: the salient results;
Conclusions.

Key Words. Three to 10 key words or phrases must be provided at the bottom of the title page to facilitate indexing. (see above)

Units of Measurement. SI units are preferred, but values may be expressed in conventional units and conversion factors indicated. The range of normal values for the reporting laboratory must be indicated. When conventional units are used in figures or tables, the appropriate conversion factor(s) must be provided in legends or footnotes.

Editing. All papers will be edited to enhance conciseness and clarity without altering meaning and to ensure conformity with journal style. Authors whose primary language is not English should obtain help from someone proficient in English spelling and grammar.

Illustrations. Photographs, line drawings, and graphs should enhance understanding of the text. Three copies of each must be submitted with the manuscript. Line drawings and graphs should be professionally prepared or computer generated and camera ready. Symbols, lettering, and numbers should be large enough to remain easily legible after the figure has been reduced to fit the width of one column. Photographs must be sharp, high contrast, black and white glossy prints not exceeding 5 inches in height × 7 inches in width. The authors must pay attention to the quality of print reproductions of x-ray plates or transparencies to assure that the special features are labeled and will remain easily visible when reduced to fit the width of one column. The name of the subject and hospital number(s) should not be reproduced in the print. Black and white copies of photomicrographs are preferred and must be cropped to a width of 3⅛ inches. The type of stain and power of magnification must be indicated in the relevant legend. Electron photomicrographs should have internal scale markers. On the back of each print and photograph affix a gum label on which the number of the figure has been written to correspond to its identification in the text, title of manuscript, first author's last name, and the word "top" and arrow to indicate the top edge. **Do not write this information directly on the print and do not mount the print on cardboard.** Illustrations which are to appear together should be mounted accordingly as plates and should be equally sized. Protect the prints by enclosing them in cardboard and separate envelopes. **Do not use paper clips.**

Every effort should be made to avoid using a photograph which includes the face or part of the face of a subject. Facial features should be marked to prevent identification of the subject unless the illustration carries details absolutely essential to the text. **In any case, a partial or full facial photograph of a** subject will not be published unless written permission has been obtained from the subject and accompanies the photograph.

Legends. Legends should not duplicate the text. Each should be on a separate sheet of paper and double spaced. Number each legend to match the illustration it describes. Illustrations mounted as plates to appear together should be accompanied by a single legend identifying the separate elements by position ("upper left," "middle") or by letters. If such illustrations have been labeled with letters, the same letters are to be used in the legend. The legend must indicate the magnification and type of stain used for photomicrographs.

Tables. Each table should be typed on a separate page, double spaced. Number tables consecutively (Table 1, etc.) to correspond to their appearance in the text. Give each table a brief title that is self-explanatory without reference to the text and type the title on a separate line below its number. Identify all abbreviations and/or symbols used in the table in a footnote.

References. All references cited in the text are to be numbered sequentially. Enclose the citation number in parentheses and place it before any punctuation, e.g., Cytomegalovirus (1), steroids (2,3), and recreational drugs (4–6) have all been implicated (7). Do not use superscripts. The reference list must be limited to works cited in the text, and numbered in the order in which they are cited. Type, double spaced on separate pages following the arrangement and punctuation style in the examples below. Journal title abbreviations must conform to those used in *Index Medicus*.

1. Brown LK. Sleep apnea syndromes: overview and diagnostic approach. Mt Sinai J Med 1994; 61:99–112.

2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1991; 324:424–428.

3. Couser WG. Glomerular diseases. In: Stein J. ed. Internal Medicine 2nd ed. Little Brown: Boston, 1987: 834–861.

List the name of all authors when there are four or fewer. When there are more than four, list the names of the first three, then *et al.*

References to personal communications and unpublished data should not be included in the list of numbered references. Instead, such information should be placed in the text in parentheses. Permission must be obtained from the appropriate individual to so quote the material. This permission must accompany the manuscript at the time of its submission. When the manuscript is accepted for publication, the author(s) will be asked to confirm the accuracy of all references.

Proofs. Proofs are sent to the corresponding author from the printer. Stylistic changes should not be made. Because of increased printing charges, the cost of author's alterations beyond routine correction of typographical errors in text and data will be billed to the author. Proofs should be corrected and returned to and received at the editorial office within 48 hours by express delivery at the author's expense to the address listed above ("Communications").

Reprint Orders. A reprint order form is sent to the corresponding author with proofs; if reprints are desired, the form must be returned to the editorial office, preferably with the proofs, but not later than 3 days to avoid late charges. A check for the exact amount in US dollars should be made out to the order of The Mount Sinai Journal of Medicine. Please indicate on the check the last name of the first author, and the title of the article. If for one reason or another, the reprint order form is not received with the proofs, it may be obtained directly from the editorial office via telephone or FAX. Reprints are available in minimum quantities of 100, at a cost depending on the number of printed pages and whether covers are desired. This information is directly available from the editorial office.

Required Form for Authors:

AUTHORSHIP RESPONSIBILITY, FINANCIAL DISCLOSURE, AND ASSIGNMENT OF COPYRIGHT

Article Title (type):

Each author must read and sign this form dealing with (1) authorship responsibility, (2) financial disclosure and (3) copyright transfer. An author who was a US federal employee when this work was conducted and prepared for publication, must sign statement (4) instead of statement (3).

1. Authorship Responsibility

I certify that I have participated sufficiently in the conception and design of this work, and the analysis of the data (where applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe that the manuscript represents valid work. I have reviewed the final version of the manuscript and approve it for submission for publication. Neither this manuscript nor one with substantially similar content under my (our) authorship has been published or is being considered for publication elsewhere, except as described in a separate attachment. Furthermore, I agree to produce the original recorded data on which the manuscript is based for examination by the Editor-in-Chief and/or his assignees should such records be requested.

2. Financial Disclosure

I certify that I do not have and have not had an affiliation or financial involvement with or in any organization or entity with a direct financial interest in the subject matter or materials being discussed in the manuscript (eg, employment, consultancies, stock ownership, honoraria), except as disclosed in a separate attachment.

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

3. Copyright

In compliance with the Copyright Revision Act of 1976, the signature of each author on this form shall indicate and be evidence of agreement and mutual understanding with *The Mount Sinai Journal of Medicine*, in consideration of the further action of the *Journal* to review and edit the manuscript being submitted, to transfer, assign, and convey all copyright ownership, including any and all rights incidental thereto, exclusively to *The Mount Sinai Journal of Medicine* if this work is published in the *Journal*.

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

4. US Federal Employees

I was an employee of the US federal government when this work was conducted and prepared for publication; therefore, it is not protected by the Copyright Act and copyright ownership cannot be transferred.

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

Return the original signed form to The Editor, The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, N.Y. 10029. Retain one copy of the form for your file. You may make as many photocopies as needed if your manuscript has more than six authors.

LEVY LIBRARY, MT. SINAI MEDICAL CENTER
3 4805 0492700 6

THE MOUNT SINAI JOURNAL OF MEDICINE

Forthcoming:

Grand Rounds

Money, Medicine and Methuselah
Christine K. Cassel
The Mount Sinai School of Medicine

Lipostasis and the Control of Body Weight: Cloning of the Obesity (ob) Gene
Jeffrey Friedman
Rockefeller University

The Lactose Permease Meets Frankenstein: New Approaches to Membrane Protein Structure
H. Ronald Kaback
Howard Hughes Medical Institute
University of California, Los Angeles

Silicone Breast Implants and Connective Tissue Disease: An Overview
Harry Spiera and Robert F. Spiera
The Mount Sinai School of Medicine

Theme Issues

Computers in Medicine
Editors: Ray Cornbill and Joseph Kannry

Laparoscopy
Editors: Barry Salky and Michael Edye

Human Immunodeficiency Virus—AIDS
Editor: Henry Sacks

Emergency Medicine
Editors: Andy Jagoda and Lynne Richardson

Religious & Philosophic Perspectives on Access to Health Care
Editors: Rosamond Rhodes, Daniel A. Moros, Allyson Robichaud

Available now:

Maternal and Infant Health: New Perspectives
Kenneth V. Lieberman and
Charles J. Lockwood, editors
volume 61, no. 5, October 1994
88 pages **$15**

Update on Sleep Disorders
Lee K. Brown, editor
volume 61, no. 2, March 1994
96 pages **$15**

Environmental and Occupational Medicine in Clinical Practice
Richard P. Wedeen, editor
volume 62, no. 5, October 1995
96 pages **$15**

The Mount Sinai Hospital
Incorporated 1852 in New York

MSM
School of Medicine
OF THE CITY UNIVERSITY
OF NEW YORK

THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 64 NUMBER 2 MARCH 1997

MAR 20 1997

Issues in Medical Ethics

Religious and Philosophic Perspectives on Access to Health Care

Daniel A. Moros, Rosamond Rhodes, and Allyson Robichaud, guest editors

STATEN ISLAND
UNIVERSITY
HOSPITAL
Affiliated with The Mount Sinai Hospital
and Mount Sinai School of Medicine

Veterans
Affairs

THE MOUNT SINAI JOURNAL OF MEDICINE

The Mount Sinai Journal of Medicine is published by The Mount Sinai Medical Center of New York and has the following affiliates: Bronx Veterans Affairs Medical Center, New York; Elmhurst Hospital Center, Queens, NY; Queens Hospital Center, Queens, NY; and Staten Island University Hospital, Staten Island, NY.

Editor-in-Chief

Sherman Kupfer, M.D.

Editor Emeritus

Lester R. Tuchman, M.D.

Associate Editors

Harriet S. Gilbert, M.D.   Julius Wolf, M.D.

Administrative Assistant

Joseline Ilagan

Assistant Editor for Housestaff

Rochelle Waldman, M.D.

Michael E. Blam, M.D.

Assistant Production Assistant

Mel Meyer

Assistant Editors

David H. Bechhofer, Ph.D.
Constanin A. Bona, M.D., Ph.D.
Edward J. Bottone, Ph.D.
Lewis Burrows, M.D.
Christopher P. Cardozo, M.D.
Mark R. Chassin, M.D., MPH, MPP
Joseph S. Eisenman, Ph.D.
Richard A. Frieden, M.D.
Frederick Friedman, M.D.
Steven Fruchtman, M.D.
Paul L. Gilbert, M.D.
James H. Godbold, Ph.D.
Richard S. Haber, M.D.
Noam Harpaz, M.D.
Tomas Heimann, M.D.
Sheldon Jacobson, M.D.
Barry W. Jaffin, M.D.
Joseph L. Kannry, M.D.
Samuel Kenan, M.D.
Suzanne Carter Kramer, M.Sc.
Mark G. Lebwohl, M.D.
Zvi Lefkowitz, M.D.
Kenneth V. Lieberman, M.D.
Lynda R. Mandell, M.D., Ph.D.
Steven Markowitz, M.D.
Bernard Mehl, D.P.S.
Myron Miller, M.D.
Edward Raab, M.D.
Elliot J. Rayfield, M.D.
Allan Reed, M.D.
Clive Rosendorff, M.D., Ph.D.
Fred Rosner, M.D.
Allan E. Rubenstein, M.D.
David B. Sachar, M.D.
Henry Sacks, M.D.
Ira Sanders, M.D.
Martin H. Savitz, M.D.
Clyde B. Schechter, M.D.
Stuart C. Sealfon, M.D.
Michael Serby, M.D.
Phyllis Shaw, Ph.D.
Alex Stagnaro-Green, M.D.
Barry D. Stimmel, M.D.
Nelson Stone, M.D.
Max Sung, M.D.
Rein Tideiksaar, Ph.D.
Richard P. Wedeen, M.D.
Vincent B. Ziccardi, M.D., D.D.S.

Editorial Board

Barry S. Coller, M.D.
Barry Freedman, M.B.A.
Richard Gorlin, M.D.
Nathan Kase, M.D.
Panayotis G. Katsoyannis, Ph.D.
Charles K. McSherry, M.D.
Jack G. Rabinowitz, M.D.
John W. Rowe, M.D.
Alan L. Schiller, M.D.
Alan L. Silver, M.D.
Alvin S. Teirstein, M.D.
Rosalyn S. Yalow, Ph.D.

The Mount Sinai Journal of Medicine (ISSN No. 0027-2507; USPS 284-860) is published 6 times a year in January, March, May, September, October, and November in one indexed volume by The Mount Sinai Medical Center, Box 1094, One Gustave L. Levy Place, New York, NY 10029-6574. Subscription price: individuals (U.S. and Canada), $75 per year; libraries and institutions (U.S. and Canada), $115 per year; individuals (outside U.S. and Canada), $100 per year; libraries and institutions (outside U.S. and Canada), $140 per year. Single copies $20. New subscriptions begin with the first issue of the calendar year. Send notice of change of address 60 days before its effective date. Periodicals postage paid at New York, NY and at additional mailing offices. POSTMASTER: Send address changes to The Mount Sinai Journal of Medicine, Box 1094, One Gustave L. Levy Place, New York, NY 10029-6574. Telephone number (212) 241-6108; Fax (212) 722-6386. Copyright 1997 The Mount Sinai Hospital.

DISCLAIMER: The statement and opinions expressed in the *Journal* by authors and contributors are solely their own and not those of The Mount Sinai Medical Center or The Mount Sinai Journal of Medicine. All advertisements are expected to conform to ethical standards, and their appearance does not imply endorsement or approval by The Mount Sinai Medical Center and/or The Mount Sinai Journal of Medicine of the products with respect to effectiveness, quality, or safety. The Mount Sinai Medical Center and The Mount Sinai Journal of Medicine do not hold themselves responsible for statements made by the authors or contributors, and for any injury to persons or property which may have resulted from ideas, products, and services referred to in articles or advertisements.

COPYRIGHT: Material printed in the Journal is protected by copyright. In accord with U.S. Copyright law, no part of the Journal may be reproduced, displayed, or transmitted in any form, electronic or mechanical, including photocopying or by any information storage or retrieval system, without prior written permission to do so. Permission should be requested from The Editor. The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574.

THE
MOUNT SINAI JOURNAL
OF MEDICINE

Volume 64
Number 2
March 1997

CONTENTS

Introduction *Daniel A. Moros, Rosamond Rhodes, and Allyson Robichaud* 71

America's Ecumenical Health Policy: A Century of Consensus- *Daniel M. Fox* 72

Religious Perspectives on Access to Health Care

A Protestant Perspective *The Rev. Dr. James A. Forbes, Jr.* 75

A Catholic Perspective *Monsignor Charles J. Fahey* 80

A Jewish Perspective *Rabbi Harlan J. Wechsler* 84

Philosophic Perspectives on Access to Health Care

Distributive Justice in Health Care *Allen Buchanan* 90

Putting the Care into Health Care *Joram Graf Haber* 96

Public Policy

The Health Care Juggling Act: Balancing Universal Access, Cost Containment, and Quality Improvement *Mark R. Chassin* 101

A Doctor's Perspective *Kurt Hirschhorn* 105

Panel Discussion 108

Program . . . Issues in Medical Ethics: March 1997—Twelfth New York Regional Conference at the Mount Sinai School of Medicine 112

ORIGINAL ARTICLES

Can Age-Based Rationing of Health Care Be Morally Justified? *Michael M. Rivlin* 113

Research and/or Training on the Newly Dead: The Jewish Perspective *Fred Rosner* 120

continued

THE
MOUNT SINAI JOURNAL
OF MEDICINE

Volume 64
Number 2
March 1997

CONTENTS *continued*

Asymptomatic Hepatopathy Is Frequent in Chronic Alcoholic Pancreatitis *Julio Maria Fonseca Chebli, Edson Lobo, Valéria Pereira Lanzoni, and Manoel Martins Das Neves* 125

Steroid Cell Tumor of the Ovary as a Rare Cause of Virilization *Halil Azizlerli, Refik Tanakol, Tarik Terzioğlu, Faruk Alagöl, and Ferhunde Dizdaroglu* 130

SEMINAR

Arrhythmias and Antiarrhythmic Drugs *Brian F. Hoffman* 136

GRAND ROUNDS

The Acute Treatment of Supraventricular Tachycardia *Marie Noelle S. Langan* 142

DERMATOLOGY NOTES

Iatrogenic Cushing's Syndrome *Neal Schultz and Mark Lebwohl* 146

BOOK REVIEWS

Future Practice Alternatives in Medicine *Stanley Reichman* 147

The Physician's Guide to Managed Care *Fred Rosner* 148

Understanding Acute Low Back Problems *Martin H. Savitz* 149

Information for Authors 150

Introduction

Daniel A. Moros, M.D.
Associate Professor of Neurology

Rosamond Rhodes, Ph.D.
Associate Professor of Medical Education
Director, Bioethics Education

Allyson Robichaud
Medical Ethics Fellow

Access to health care has been vigorously debated in the United States during the past 4 years. In the first 2 years of the Clinton Administration (1993–1994), proposals for universal health insurance competed with more narrowly focused efforts to simply reduce the growth of health care expenditures. The push for some form of universal health care also came into conflict with the desire of conservatives to reduce the imposition of the Federal Government on everyday life.

In the United States, as in other industrialized nations, the twentieth century has been characterized by greater access to health care for a larger percentage of its citizens. Access to health care has increasingly been viewed as a citizen's right and a government's responsibility. At this point, however, the United States is the only developed nation that does not provide all of its citizens with access to health care.

In the American dialogue of the 1990s, while political philosophers, bioethicists, and economists thrashed over the topic in terms of rights, duties, justice, and utility, religious groups were relatively silent on the issue of universal access to health care. Remarkably, religious perspectives have done little to shape the debate. This is all the more surpising when we consider the historical and central role of organized religion in providing health care to the poor. Throughout the nineteenth century and the first two thirds of the twentieth century clinics and hospitals affiliated with and supported by religious groups were crucial providers of charitable care.

"Issues in Medical Ethics: 1996," the eleventh annual New York Regional Conference, focused on religious and philosophic perspectives on access to health care. It was concerned with the role that philosophic and religious discourse can have in shaping the debate. The conference brought together a multidisciplinary panel of historians, theologians, philosophers, and physicians to consider the content and conduct of our public discussion. Papers by Protestant, Catholic, and Jewish theologians and academic philosophers presented the key perspectives on the issue. This core was framed by an opening presentation by Daniel Fox who examined the changing position of religious organizations on the question of universal access to health care. Additional philosophic perspectives were provided by Allen Buchanan and Joram Haber. Closing remarks by both Mark Chassin and Kurt Hirschhorn addressed current public policy and medical practice. Thus, the conference was structured not only to challenge organized religion to confront the problem of health care access, but to provide important material to physicians and policy makers and to engage them in scholarly discussion. In publishing these papers from our 1996 conference, we hope to contribute further to the public debate on the issues of access to health care and control of health expenditures. These are issues that will continue to challenge us for years to come.

Issues in Medical Ethics: 1996

America's Ecumenical Health Policy:

A Century of Consensus

Daniel M. Fox, Ph.D.

In the United States during the past century, organized religion has been less important than civic religion in decisions about who received health care. We had a national consensus about the goals of health policy that was justified by our civic religion. I call that consensus ecumenical, stretching the usual definition of the word, to emphasize the consequences of the erosion of that consensus. If the leaders of organized religion do not react against the increasing commercialization of health care in this country, very few other Americans will be inspired to react against it.

Since the 1890s, most people have believed that medical science has made continuous progress against dread disease. Belief in the power and effectiveness of medical science became a major theme of our civic religion. Other fundamental doctrines of this civic religion were individualism, competition, and the superiority of the American standard of living. Belief in the power of medical science was ecumenical because it was shared by and triggered vast spending from each of the major religious communities in this country.

The consensus about the power of medical science originated in the second half of the nineteenth century. During those years, pioneering bacteriologists identified the causes of the most threatening diseases. These new findings about the causes of disease stimulated optimism that the next steps in the progress of medical science would be discoveries about how to prevent and cure these diseases. Pasteur devised a cure for rabies, a disease that caused enormous pain and death. People came to Paris from all over the world seeking his cure. Lister and other surgeons devised antiseptic and aseptic procedures that reduced the infection and death that resulted from operations. Doctors and nurses, following the findings of Semelweis, used carbolic acid to kill germs that caused them to transmit infections to women during childbirth. In the mid 1890s, a new antitoxin against diphtheria saved thousands of children from ghastly deaths by suffocation as a result of their infection.

These advances benefited millions of people. They also had enormous symbolic effects on health policy. By health policy I mean the ways in which the public and private sectors organize the financing of services and enable people to receive them.

The basis of health policy for most of the twentieth century has been the belief that the methods devised to control infectious diseases, which have been the major cause of death throughout history, would be improved and generalized to the control of chronic degenerative diseases. For a half-century before the proliferation of antibiotic drugs in the 1940s, most people who made health policy believed that these drugs would soon be discovered. For a generation after the first widespread use of penicillin in the Second World War, most people who made health policy believed the progress of medicine would transform everyone's life. Most experts believed that this transformation would occur because the methods that were eliminating the scourge of infection would gradually reduce the incidence and severity of chronic disease. As early as the 1920s, the use of insulin to control diabetes demonstrated that effective treatments for chronic diseases could be found. The promise of medical science, in sum, exceeded its splendid performance.

In the United States, four overlapping groups have made health policy and then thrived on the

---

Address correspondence to Daniel M. Fox, Ph.D., President, The Milbank Memorial Fund, 645 Madison Avenue, 15th Floor, New York, NY 10022–1095.

policies they made. The first group is what we now call the nonprofit sector; a century ago, when our consensual health policy took shape, this group called itself religion and philanthropy. This sector built and operated hospitals and universities and paid for services for persons in poverty. The second group is the business sector, employers, and labor unions. This sector has paid for most of the health services that have been consumed for the past half-century through profits and wages foregone. The third group is government. Through their tax policies, the federal government and the states have subsidized the expenditures of the nonprofit sector. Moreover, by foregoing taxes on profits and wages spent for health insurance in the business sector, the federal government provided an enormous subsidy for the purchase of health services. Through social insurance (insurance that is paid for by all persons with jobs), the federal government has guaranteed health care for elderly and disabled persons. By direct appropriations, federal, state, and local governments have paid for health care for millions of people. These appropriations have exceeded charity as a source of payment for health care for the past six decades. The federal government also has paid for most biomedical research. Government on all levels, moreover, has invested substantially in building and operating hospitals and subsidizing the cost of higher education for the health professions. The fourth group is the medical profession. Courtesy demands that I include other health professions, but political reality is contrary to courtesy. Because the leaders of the nonprofit, business, and government sectors trusted them for most of the past century, physicians have had a major, often determining, voice in health policy. That voice was justified by the belief in the power of medical science, but it was much more than that. The basis of trust also was the belief that most physicians, in most circumstances, accorded priority to their patients' interest over their own. Rarely has any occupational group acquired so much goodwill and maintained it as long as American medicine has.

The memberships of these groups obviously overlap. Policy making is complicated. But there is considerable evidence that, complications aside, health policy in this country has usually been made by people who run for office, meet payrolls and negotiate about them, and treat patients. These people negotiate about who receives which services from whom, at what cost, and about what cash flows from whom to whom.

This health policy has not been policy by conspiracy. Almost everyone I have mentioned has been accountable to someone: voters, stockholders, congregants, members, colleagues, neighbors, and so on. American leaders have not had to conspire because they served a broad public consensus. Their purpose was to improve the health of the public and to reduce the suffering of individuals through the progress and application of medical science.

A culture can often be understood through its jokes. Everyone knows a variation of the one about the person who grew up in Scotland where death was imminent, migrated to Canada, where it could be postponed, and then lived in California, where it had become an option.

Congressional leaders told us, in 1994, that we are living in an age of revolution. All of us are experiencing the revolution in health care. I will not attempt to describe the revolution or its causes; that is for another occasion.

What is worth paying attention to, however, is how people describe the revolution in health care from their own point of view. Recall these familiar words: managed care, downsizing, consolidation, integrated systems, preferred provider, risk contracting. None of these words or phrases have anything to do with the advance of medical science, or with increasing access to services that can prevent or cure disease or reduce suffering. These are the words of markets, of the production of goods and services for commercial purposes.

In this decade reformers of all political persuasions, as well as persons opposing reform, have described health care as a product, a commodity. The Americans who talked to pollsters accurately perceived that the Clinton Administration's health reforms (and most of its competitors) dealt less with security and health than they did with ways to fix an industry. People have a broader range of opinions about whether to fix an industry and how it might be fixed than they do about their security or access to basic services. Their opinions about fixing any industry, moreover, include the view that such discussions are boring.

We have, then, a new consensus about health policy that appears to be gathering adherents. That consensus begins with the assumption that health services are commodities. We take our bodies in for repair just as we take in our cars.

The new consensus has gradually replaced the old one. In the old consensus, access to health care was important because our civic religion taught that medical science would gradually enable people to be healthier and happier. In that old consensus, the institutions of health care were more like churches than they were like garages.

In the emerging consensus, health services are just another set of consumer goods. Markets are the best mechanism to supply consumer goods and to meet the demand for them. Because of the efficiency of market mechanisms, nonprofit and government institutions are impediments to efficiency.

Many people are saying that nonprofit institutions and, of course, government hospitals and health plans should be reorganized. Consider the flaws of nonprofit institutions as they are reported in the "Wall Street Journal of Medicine" and elsewhere in the financial press. Nonprofit organizations lack access to equity capital. They produce lower rates of return than more efficiently organized providers of care. They have volunteer boards whose members have many distractions. They are under increasing pressure from tax-collecting officials and state attorneys general to document the benefits they confer on their communities.

In contrast, the investor-owned health care sector can transform health care. Investor-owned organizations, for example, can sell stocks and leverage that investment, press for higher profits, force management and physicians to account to ownership, avoid dubious benefits to the community, and remove excess costs (and also cash) from the health industry.

A health sector that has been sufficiently commercialized may not be able to perform other social tasks, of course. For example, its institutions and their staffs of highly trained professionals may not resolve potential conflicts of interest in favor of patients and consumers. They may decide that making money is a higher value than making patients comfortable. The institutions in a commercialized health sector may decide that the goal of competition is to acquire a sufficiently large marketshare in a particular city or region in order to charge monopoly prices and not have to worry about other providers offering to make patients healthier or more comfortable.

However you judge the commercial motive in health care, whatever your opinion is of markets as the route to efficiency, such commercialism may not be compatible with the motives and purposes of religion. Curing and caring may be marketable only in limited ways. People may seek qualitatively different assistance and assurance from their physicians than they do from automobile mechanics. Providers of health care might be expected to meet different standards than car dealerships.

I have talked about organized religion and health care, but not about organized philosophy because I hold the dim view that organized philosophy became one of the last subspecialities of medicine during the years of high life on the reimbursement rate that preceded our current era of reorganization and/or retrenchment. What floated in on the high tide of reimbursement is likely to float out when that tide changes. By organized philosophy I mean professionals with advanced degrees in that subject who practice bioethics and moral philosophy. Organized philosophy must be separated from issues of justice, rights, charity, and virtue. These issues have been addressed in health policy for centuries, generally with reference to organized religion, civic religion, or both. In the 1950s and 1960s several theologians and a few philosophers began to focus on health care, and that attention became the modern bioethics movement.

Bioethics has been to medicine as arms control and disarmament were to the Cold War. That is, bioethicists have been respected, widely quoted, and often paid reasonably well, but they have been functionally marginal to what has become, like it or not, the business of American medicine. In making this claim, I am neither criticizing philosophers nor endorsing commercialism. I am simply saying that religion, organized and civic, has a great deal more to do with the kind of health care that Americans have.

For centuries, religious institutions and their leaders engaged in agriculture, supported armed forces, made foreign policy, and were high rollers in the art industry. Religious institutions have gradually ceased being central to these areas of public life. Health care may eventually be added to the list of activities in which religion has a history but neither a present nor much of a future. Or it may not. Although the charitable and nonprofit sector is dissolving around us, organized religion may rally. Stalin is supposed to have sneered that the Pope had no troops. Wrong. Religious institutions still control billions of dollars in assets in health care and, more important, they enjoy the respect of millions of Americans. It is possible that an alliance of organized religion and a re-professionalized medical profession can contain the commodification of American health care . . . Possibly, but as a practical person, I must bet that it is unlikely to happen. I'd like to lose this bet.

Religious Perspectives on Access to Health Care:

A Protestant Perspective

The Rev. Dr. James A. Forbes, Jr.

Brothers and sisters, I am grateful for this opportunity to be engaged in conversation about access to health care and, more particularly, to represent a Protestant perspective on the issue. My approach to such an assignment is shaped by my involvement in an interfaith conversation on these matters. For the past 2 years Union Theological Seminary, Jewish Theological Seminary, and Columbia University School of Public Health have been meeting to address the moral and ethical implications of the national health care reform debate. From this rich in-depth exchange of ideas, it has become clear to me that it is increasingly difficult to distinguish among Protestant, Catholic, and Jewish understandings. We have had an impact on each other's consciousness to such an extent that we should be very cautious when we attempt to identify the primary source of insights and ideas.

My responsibility to speak as a Protestant is a most demanding one because of the almost infinite number of opinions which claim to reside in the Protestant household. Consider some of the elements of the following extended definition from the *Concise Oxford Dictionary of the Christian Church* (1):

> Protestantism is the system of Christian faith and practice based on the principles of the Reformation. Common to all its denominations are (1) the acceptance of the Bible as the only source of the revealed truth, (2) the doctrine of justification by faith alone [Let me add the word "grace" at this point.], (3) and the universal priesthood of all believers. Protestantism has tended to stress the transcendence of God over against the finiteness of humanity which lives out the effects of the "fall": "Original Sin." Protestantism puts emphasis on the impotence of the unaided human intellect to gain any knowledge of God. It minimizes the liturgical aspects of Christianity and puts preaching and hearing of the Word before sacramental faith and practice. While it has rejected asceticism it has upheld for the individual a high standard of personal morality. The principle of private judgement in the interpretation of scripture accounts for the variety of sects and churches typical of Protestantism, in which many shades of doctrine and practice are found.

Now you see why my assignment is a most formidable task. We say of love that it is a "many splendored thing." Of Protestantism we say that it is a "many splintered thing." Now that you know the degree of difficulty of my task, I proceed with cautious humility.

When I wish to apply the tenets of my faith to a contemporary problem I am guided by the wisdom of the Protestant theologian, Paul Tillich, and also a tradition of discernment from my African past. In his first volume of *Systematic Theology* (2), Paul Tillich sets forth what he calls the "principle of correlation." The questions in one's existential situation are correlated with the answers in the faith tradition or the Gospel. This suggests a two-way dialogue, an alternating exchange between text and context in which the truth of authentic being and action may be found. How this principle works is dramatically preserved in a ritual of the Yoruba religion centered in Nigeria. When a priest is asked to respond to a particular problem, the priest works with the client in a shared quest for the wisdom of the "orisha" or spirit. The priest hurls a divining chain onto the ground. From the configuration of cola nut shells on the chain the priest determines the sacred number of the poem which should be read

---

Senior Minister of The Riverside Church, Harry Emerson Fosdick Adjunct Professor of Preaching, Union Theological Seminary, New York, NY. Address correspondence to The Rev. Dr. James A. Forbes, Jr., The Senior Minister, Riverside Church, 490 Riverside Drive, New York, NY 10027.

or quoted out of the 256 poems of sacred Yoruba literature or scripture. The priest quotes the poem and asks the person who seeks advice to identify the point in the recitation which is relevant to the presenting problem. Together the priest and the client discuss the implications of the revealed insight for the problem at hand. This is the Tillichian principle of correlation at work.

The question before us is: Who should have access to health care services in the light of the fact that [1] there are limited resources, [2] some persons lack the power to command care, and [3] there is a need to develop just principles for the distribution of limited resources.

The way I want to approach this is to address particularly the issue of the mandate to show compassion to the poor, to include them in the consideration of access to health care. Knowing that this is only one aspect of what we will be talking about today, I have chosen to emphasize this element because I have a sense that access to health care for all of us is related to how we respond to care for those who are called in the Gospel of Matthew 25 (3), "the least of these." Then, at the end of my conversation, I would like to speak of accessing hidden resources for healing which I think will be helpful to each one of us.

When one invites a Protestant preacher to speak, the chances are you will hear some preaching! The hope is that there will be relevance in that preaching to the issues and policies under consideration. So I take this opportunity to offer some homilectical fragments. Then I will underscore some basic principles. In the process, as Protestants are wont to emphasize, I dare to believe that something of inspiration is necessary to move us to faithful action on the frontiers of what we have already affirmed. I have thought about several sermonic approaches. I could talk about greed, for example, because we all understand that greed, no matter how we speak of it, is somewhere at the heart of the maldistribution of resources and of limited access to health care. For this topic I could have used the sermon I preach sometimes entitled, "You Cannot Serve God and Mammon." I would say that in making a primary choice to allow money to be the deciding factor in our decision making, we surrender the opportunity to pursue the depths of commitment to which the faith calls us. But I think I will not dwell on that one.

A second topic of crucial importance is the issue of who will be granted access to limited resources. For this one I would want to read a section from the Bible that informs a particular aspect of my Protestant heritage. It is, in fact, a value reflected in most religious traditions. So from the seventh chapter of Matthew verses 7 to 12, we read:

> Ask and it will be given you. Search and you will find. Knock and the door will be opened for you. For everyone who asks, receives and everyone who searches, finds and for everyone who knocks the door will be opened. Is there anyone among you who, if your child asks for bread will give a stone or if the child asks for a fish would give a snake. If you then who are evil know how to give good gifts to your children how much will your father, [or heavenly parent] give good things to those who ask him.

And then Matthew 7:12:

> In everything do to others as you would have them do to you, for this is the law and the prophets.

So from a Christian Protestant perspective, central to any faith commitment must be this "golden rule." And so sometimes I preach a sermon entitled, "Whatever Happened to the Golden Rule" which is the question to be raised in connection with every aspect of our health policy.

There is a popular story with some relevance here: A boy was asked, "What is faith?" He responds, "Faith is acting on what you know isn't true." This passage says, ask, seek, and knock; and then it promises that the door will open, you will find what you are looking for, and you will be given an answer. But we who live out of the Protestant tradition understand that we live between the tensions of our projected ideals of God and the coexisting patterns of reality. Many people today are asking and not receiving what they need; many people are searching and they will never find; and many are knocking on doors of access not open to them. We live out our mandate between the realities of our world and the stubborn vision of a time when the realm of God will be such that we will behave as children of God responding to the needs of each other. How will we get there? Therefore, if the sermon does not speak of how one moves between the "is" and the "ought" then perhaps the sermon is so much inspiration, the perspiration from which will dry before we get to policy making. So lets get down to the section that I want to consider for today.

I invite your consideration of a theme from a sermon entitled, "Health Care for the Least of These." This is a message that reflects the best understanding within my own Protestant background which was largely informed by Christian Realism taught by my professor, Reinhold Neibuhr, in the days when I attended Union Theological Seminary. I hope what I say will provide some insight into the policies in pursuit of our approximation of justice and compassion, which was what Neibuhr wanted us to recognize, that the kingdom is not likely to appear in New York, not in this millennium. It will take the next millennium as well to begin to approach it. So let's have a little more sermonizing here.

Congressional subcommittees may debate the wisdom of extending health care coverage to all citizens. For them, it may be a matter of political expediency or loyalty to lobbyists with deep pockets. But for those who read Amos 8 and Matthew 25 and try to live by the challenge that these texts hold before us, the consideration of excluding someone is a life and death issue. Amos, whose name means "Burden of the Lord," prophesied against insensitivity to the needs of the poor. Great calamity was surely coming to those who bring suffering to the poor of the land. It will be dark in the daytime. Feasting will be turned into mourning. Songs of joy will be turned into lamentation and woe. It matters to God how we treat God's other children. While the health care debate shifts from single payer to managed care, to health maintenance and preferred provider organizations, regional alliances, and national boards under government auspices, every Christian should read Matthew 25:31–40. And if there is no emerging clarity about what Christians ought to do, read through verses 41–46. Now, that is no edifying discourse. It is down-right threatening to those of us who take the Bible seriously. And for those who don't, at least give the word a hearing today. It matters to God how we treat God's own children. This text, in the spirit of Amos, sets forth some fundamental expectations to those of us who call ourselves Christians. Notice, Protestants make good use of the Hebraic foundation of our tradition. In Amos, consider the first point. We are expected to know that the good life is to be lived in accountability. We are responsible for how we live, how we treat ourselves, and how we treat others, both friends and foes. There is a relationship between the seeds of action we sow and the harvest of good or ill that we reap. A day of reckoning is coming. A record is being compiled. It is not just jolly old Saint Nick who is making a list and checking it twice to see who is naughty or nice; life itself keeps a record. It is stored largely in our spirit, shown in our character, insinuated in our relationships both public and private. To drive the lesson home in the sharpest contrast, we are told that a day of judgment is upon us. My conviction is, and this is an aside, that we are living under the day of judgment, occasioned by patterns of our own choices regarding who will have access to the resources of God's good earth.

Now in Jesus' story in the 25th chapter of Matthew, the judgment becomes very, very present. The Son of Man gathers all the nations: not just persons, but nations. Then there is a great separation, left and right. The sheep on the right hand and the goats on the left. Now to those on the right hand, God says: "Come, O blessed. Inherit the kingdom prepared for you from the foundation of the world. For I was hungry and you gave me food. I was thirsty and you gave me drink. I was a stranger and you welcomed me. [And some of us will add, I was in the hospital and you visited me]. I was naked and you clothed me." And when the people asked, "Lord when did we do all these things," the answer is given, "truly I say to you, as much as you did it to one of the least of these my brothers and sisters, you did it to me." But the ones on the left will be told, "Depart from me you cursed into the eternal fire, prepared for the devils and his angels. Truly I say to you, as you did it not to the least of these you did it not for me." And they will be taken away for eternal punishment and the righteous into eternal life. Now brothers and sisters, what I think is very clear in this text is that solidarity with the poor and the deprived is at the heart of one's responsibility. So close is the relationship that what is done for the poor is also done for the one whom Christians call Lord. The glorious principle of interchangeability is articulated here. And our assessment of our own morality and ethics in policy making and delivery of services has to be based on the truth that what you do for the least of these you do to the one you consider the greatest. Although one might be ever so attentive to the needs of God's anointed one, and yet fail to minister to the seemingly insignificant person, one has not shown due reverence to the messenger of God. It matters to God how we treat God's own children. Let the politicians or the preachers or the pharmaceuticals or the medical technology industry or the hospital administrators or the medical practitioners overlook the least of these to their own peril. This is hard, hard preaching. It matters so much that Liberation Theologians seek to make the case that God, indeed, has a preference for the poor. And God urges us to stand in solidarity with them for their deliverance from the chains of oppression. An ancient proverb claims that God fans the flies for the cow that has no tail. A liberationist would interpret this as God's preference for the poor. Indifference to the plight of the poor is a tell-tale mark of moral deficiency. To claim to care and not to act is hypocrisy. From the perspective of faith it is blatant lying. Quickly, get the word to the decision makers, the policy makers, those inside and the outside the Washington beltway. Call the city hall and tell them, "Be careful how you treat the least of these." Read the part of the Declaration of Independence declaring that all men and women are created equal and are endowed by our Creator with certain inalienable rights among which would be life, liberty, and the pursuit of happiness. Tell everybody it matters to God how we treat God's children. Thus ends the sermon.

What are the implications? We must move beyond religious rhetoric. It was once my plan to promote the "Golden Rule Health Care Plan." Recently I discovered there is actually a company presumably founded on this concept in California. I am told that it is not fully sensitive to the needs of "the least." How easily these titles can be coopted. Protestants keep talking about reformation and urge that it must be an ongoing process. This suggests that we have to reclaim what the Golden Rule Health Care Plan means. I think it would include some of the following:

1. We must view the issues of national health care from the perspective of what we believe God wills for all our fellow citizens. Then the question becomes, how do we bring the things that we know to be true to have an impact on policy? In terms of ethical and moral principles we should begin with the biblical admonition that we measure our faith by what we do for the "least of these."
2. We must provide service for others on the basis of what we would wish for ourselves if we were similarly situated. Once again, a religious truism. But revolutionary if policy makers would take it seriously.
3. We must approach our care for others out of the recognition that quite possibly the privileges we enjoy may have inadvertently occasioned the impoverishment and powerlessness of others. In one of his sermons Paul Tillich reminds us that our "having" cannot be divorced from others "not having."
4. We must be willing to invest resources for the creation of a caring and just society by reexamining a just rationale for pay for work, the adjusting of wages and costs according to more democratic and humanizing principles. We must hold the free enterprise system accountable to social responsibility for the common good. All of these measures constitute what I would like to call an "integrity tax." And because my name is Forbes, I do want to distance myself from the flat tax and speak of an integrity tax. If we believe in democracy, integrity demands that we share the cost for the achievement of the ideas. The only kind of economic system worth believing in is one which is able to make provisions for the "least of these." We must take seriously the continuing call to provide at least subsistence necessity. I call it minimum standard of human decency. Instituting an integrity tax is what I believe has to happen to counterbalance the spirit of greed. We, who speak out in the religious tradition, and who wish to maintain our standing on moral and ethical grounds, will have to tell the people who want a health care system providing access to all, that it cannot be discussed until they are prepared to say, "We believe strongly enough in this level of access and inclusion that we wish our taxes to be the primary stream providing resources for the system of health care we promote."
5. We must promote a more comprehensive definition of health and encourage multidimensional approaches and a variety of alternatives for prevention of illness and for acute and chronic care. Guardians of the recognized professions, indeed, have a responsibility to protect the public against irresponsible and harmful practices. Occasionally the negative critique leveled against alternative approaches seems motivated by efforts to safeguard market share rather that to provide a scientific basis for discrediting certain practices. The greed of some practitioners may be a significant factor in closing the door to less traditional methods, which some persons may find helpful and more accessible.
6. We must enlist panels of competent practitioners to address the moral issues related to health care such as just allocation of limited resources, regulation of just structures of distribution of care, and medical ethics in areas of research and technology.
7. We must move beyond ideological and political fixation on the merits or demerits of private versus public and governmental capacities for efficient administration. We must mandate a bipartisan task force to devise a plan which combines the strengths of multiple sectors and institutes safeguards against the alleged and often proven weaknesses of the various sectors.
8. We must begin to make plans for a transition from our present health care delivery system to one that is more inclusive and efficient. There ought to be a level of comprehensive long-range planning which anticipates the need for vocational and technical conversion.

Resistance to changes in policy and practice may be somewhat reduced if thoughtful attention is paid to the needs and interests of those who currently make a living under the present arrangement.

9. Just as the nation has been assured in the past that we have the capacity to mobilize for war, let us reassure one another that we are able to mobilize for health for all. We need to cultivate a "can do" mentality.
10. As a plan is devised for the health of all citizens, a process of education must be launched to teach the wedding of rights and responsibilities. As we all learn the virtues of compassion and "neighborism," we should have the courage to believe that our God will aid us in our efforts to show forth love and justice for the common good.

Now let me close by saying some words of inspiration from a Protestant perspective. I think of my mother as a theologian. In fact, because of my mother's wisdom and care, I think I understand God a little bit better. In the house of my upbringing, there were eight children. Usually, we would gather for dinner each day. When we met, my mother had a ritual at the table. She said, "I am getting old, I cannot keep up with all of you." But when we got ready to say the blessing, my mother would ask, "Are all the children in? Are all the children in?" And if someone was missing we would be required to prepare a plate for the missing person, put it in the oven, and keep it warm until that absent person arrived. I think that is like Mama Eternal. Mama Eternal, with respect to the health care situation, always asks the question, "Wait, are all the children in?" Second, my father was a minister in the Pentecostal tradition and he prayed for me one day when I had a fever. I was really sick, delirious in fact. And putting his hand on my forehead he prayed, "Lord this is my son, you know what to do, you understand his situation, won't you heal him please?" He took his hand off my forehead and I felt that air conditioning had been turned on. I immediately got up and was ready to go outside to play. And that impressed me. And what I always wanted from that day on was healing hands like my daddy. Now the Protestant perspective is that it isn't simply professional priests who are called to be healers. The "priesthood of all believers" means that each of us, from wherever we come, is called upon to have healing hands. But we need healing hands in the community, not only for our family members. This requires policies that are based on a determination to respond to the tension that exists between the realm of God where all are healed and the reality where many are left out, even today. Finally, there is a story I tell every time I speak on health care, because it really captures what I think is the most important contribution I can make. One Sunday afternoon while preaching I received a call to go to Sister Baldwin's house. She was having nose bleeding. We got together and drove over to her house. When we arrived at her house, there was blood all over the place. We surveyed the situation and then went to work. One of the members who was with me took a medicine bottle, caught three drops of Sister Baldwin's blood, put the cap back on the bottle and placed it on the cupboard, explaining, "This is what my grandmother used to do when we kids down in Pitt County, North Carolina had nose bleeds." Sister Coleman found a brown paper sack, tore off a piece, rolled it up, and stuck it under sister Baldwin's lip. Sister Randolph got some ice and applied an ice pack. And I laid my hands upon Sister Baldwin and prayed a preacher's prayer asking God to heal her. In about one minute the nose bleeding stopped and we went back to the church. Our only problem was we didn't know which method had worked. Now the thesis I offer is this, I don't think any of our individual methods did the trick on that occasion. But in our willingness to respond, out of such insights and giftedness we possessed, an augmented dynamic of healing was made available to that situation. This is the thesis I offer. I hope that each one of you is ready to be recruited for the work of using your healing hand for the health of all God's children in the nation. When the economists, lawyers, insurance companies, medical technologists, pharmacists, doctors, nurses, administrators, and preachers and teachers develop a deep consciousness that God cares for the health of all, then we will find increased access to health and wholeness for all our fellow citizens.

References

1. Livingston E, editor. *The Concise Oxford Dictionary of the Christian Church*. New York: Oxford University Press, 1977: 419.
2. Tillich P. *Systematic Theology*. Chicago: University of Chicago Press, 1957: 8.
3. *Bible*. New Revised Standard Version (NRSV).

Religious Perspectives on Access to Health Care:

A Catholic Perspective

MONSIGNOR CHARLES J. FAHEY

A Personal Note

I HAVE FOUND THIS ASSIGNMENT to be simultaneously interesting, pleasant, and frustrating. Personally, it has been interesting because it gave me the occasion to review what I have come to take for granted and allowed me to reflect on concepts that have become part of my being. It is frustrating because so many of my fellows either do not know about the amazingly consistent practice and teaching of the Church in this regard or don't pay any attention to it, but then we are the church of Mother Theresa and Pat Buchanan, Cardinal Bernardin and Michael Novak, Dorothy Day, Popes John XXIII and John Paul II. This is intensely personal, because for the past 36 years a significant part of my time, effort, and energy have been invested in adding to and refining this tradition, making it applicable to contemporary society both in the development and operation of programs and in the development of public policy at the state and national levels, and even in developing and maintaining programs and agencies which are responsive to its challenge.

As many of you know, for 18 years I was in Catholic Charities in the Syracuse diocese which has extensive health programs. For the past 18 years I have been at Fordham's Third Age Center, which focuses its activities on health care, albeit for those in the Third Age. During the entire period I have been privileged to be involved in various Church-related policy development processes as well as participate in various state and national public policy groups. I have to confess that in the public forum I have continually "translated" the theological and religious perspectives into more secular language, even as I have attempted to assimilate the considerable insights and lived experience of wonderful colleagues in the community and in turn translate them to enrich the reflections of theologians and to influence the thinking of Church leadership. Thus, this project has been a stimulus to reflection and a labor of love.

The Basic Teaching

There are two official statements that reflect both the past and current teachings of the Catholic Church internationally and nationally in the matter of access to health care. In fact the teaching has been so consistent that I could well end my remarks at this point. The following excerpts are from "A Pastoral Letter of the American Catholic Bishops, Health and Health Care" issued November 19, 1981 (1).

> Every person has a basic right to adequate health care. This right flows from the sanctity of human life and the dignity that belongs to all human persons, who are made in the image of God. It implies that access to health care which is necessary and suitable for the proper development and maintenance of life must be provided for all people, regardless of income, social or legal status. Special attention should be given to meeting the basic health needs of the poor. With increasingly limited resources in the economy, it is the basic rights of the poor that are frequently threatened first . . .
>
> The benefits provided in a national health care policy should be sufficient to maintain and promote good health as well as to treat disease and disability. Emphasis should be placed on the promotion of health, the prevention of disease and the protection against environmental and other hazards to physical and mental health . . .
>
> Health planning is an essential element in the development of an effective and coordinated health system. Public policy should ensure that uniform standards are part of the health care delivery system . . .
>
> Following these principles and on our belief in health care as a basic human right, we call for the development of a national health insurance program.

In Pope John XXIII's encyclical, *Pacem in*

Address correspondence to Monsignor Charles J. Fahey, Marie Ward Doty Professor of Aging Studies, Senior Associate, Third Age Center, Fordham University, Bronx, NY 10458.

Terris, medical care is listed among those basic human rights which flow from the sanctity and dignity of human life (2).

The Evolution Of Concern

The Church's concern for and involvement in health care has been constant since its beginnings. As society has evolved, so has its participation. Initially the Church was concerned primarily in the area of pastoral care and sacramental ministry. Gradually its members, especially those who banded together in religious orders, began to directly provide health-related services. The Church has always been involved in what we now call medical ethics. In the latter part of the nineteenth century, with the modernization of society, the church became interested in the structures of a just society including, but not limited to, health care for all. Even as medicine and health care evolved, so did the Church's concern about justice in the provision of health care.

The basis of this involvement is the word and work of Christ who was preeminently a healer of body and spirit. His ever challenging moral admonitions in the Sermon on the Mount, the portrayal of the general judgment, and the parable of the good Samaritan are familiar to all of us. When the disciples of John the Baptist asked if he were the long awaited one, He said, "Tell them what you have experienced: the blind see, the lame walk, those who suffer from virulent skin diseases are cleansed and the deaf hear, the dead are raised to life and the poor have the good news preached to them." (Luke 7:22,23)

Historical Notes: Provision of Care

Although health care as we know it is a relatively modern phenomenon growing concurrently with the scientific advances and their applications to modern medicine, the care of the frail and vulnerable has long been seen as integral to the life of the Church. Numerous religious orders were founded precisely to care for the sick and the dying. Basil the Great founded a hospital in 372 in Caesarea (Kayseri) in his diocese of Cappadocia.

Benedictine monasteries included infirmaries. Monks were acquainted with the works of the Greek physicians, copying and translating into Latin their manuscripts, and in their gardens planted herbs used as medicines for the restorations of many illnesses. . . . the Sisters of the Holy Ghost, originally a lay society, founded the city hospital in Rome in 1204. The community of sisters who founded the Hotel Dieu de Paris and later adopted the rule of St. Augustine is the oldest extant order dedicated specifically to nursing. These Augustinian nuns were committed, in addition to poverty, chastity, and obedience, to a fourth vow, the care of the sick poor (3).

Three religious orders with European roots have had a significant role both in programs and policy in the United States: the Alexian Brothers, whose initial focus was on burying the dead and taking care of the "insane"; the Religious Sisters of Mercy; and the Sisters of Charity. Our city and nation see evidence of their work even in areas which had or have small Catholic populations. St. Vincent's, Cabrini, St. Clare's, Bayley Seton, Mary Manning Walsh, the Catholic Medical Center of Brooklyn and Queens are integral parts of the tapestry of New York City's health care.

To have some idea of the magnitude of this enterprise the Report on the National Convocation of Catholic Healthcare Leaders (4) noted:

- More than 150 years of commitment and service
- 622 Hospitals in 48 states
- 714 long-term care facilities in 47 states
- Thousands of community-based programs
- 16% of U.S. community hospital admissions.

Not without controversy, but none the less, with real generosity of spirit, we have experienced the willingness of these and other institutions to respond to the AIDS crisis. The Profile of Catholic Healthcare 1995 indicated that Catholic Hospitals constitute 10.3% of the Nation's hospitals, 15.6% of its beds, and 16.1% of the country's admissions. Total revenues in 1993 were $40.7 billion, assets were $44.1 billion, and fund balances were at $22.7 billion (5).

I have been privileged to be a trustee/director of the Sisters of Mercy Health Care System of St. Louis. It was founded by a wonderful group of women who left Ireland in the middle of the nineteenth century and developed hospitals in such places as Laredo in Texas, Oklahoma City and Fort Scott in Kansas, and Fort Smith in Arkansas. One of the most fascinating stories involves their presence in Vicksburg, Mississippi, hardly a center of Catholicism. Before the Civil War they had started a hospital and a school which operated through the 1980s. In 1990 it became clear that Vicksburg did not need two acute care hospitals each of some 200 beds, each at 50% occupancy. The Sisters of Mercy System offered to purchase the proprietary hospital "across town" but was unsuccessful. Painfully, it was decided that it would further the common good to close our facility. You can imagine the anguish after 150 years of service. However, the health system has taken the resources which would have been expended in this area and has committed them to ambulatory care in the Mississippi Delta.

Even though Catholic health care has become more systematized, the charisma of the founding institution is tapped to generate resources and deploy them to underserved areas at home and abroad.

Health Care and Society

On May 15, 1891 Pope Leo XIII published his famous *Rerum Novarum,* an encyclical letter on the condition of Labor. It was the first of a series of formal papal statements addressing the organization of modern society. They exhibit the same basic themes: the right of the worker to a decent wage and to organize collectively to achieve it and decent working conditions, the conditional right to private property, the importance of the common good and its promotion, the importance of social justice to the individual and to a peaceful society. In recent documents there has been an emphasis of human being's role as steward of the earth. *Quadragesimo Anno* of Pius XI on Reconstructing the Social Order, John XXIII's *Pacem in Terris* and *Mater and Magister,* Paul VI's *Populorum Progressio,* and John Paul II's *Sollicitudo Rei Socialis* all strike the same theme.

Concurrent with these broad pronouncements about the just social order and increasing public attention to health and environment was the dramatic evolution of the Catholic Health Association (the Catholic Hospital Association) (CHA). Under the leadership of its first lay president, Jack Curley, and with the prodding and encouragement of religious sponsors and their leaders, CHA has become an important factor in health care reform. With an extraordinary competent public policy staff, led by William Cox, the Association published a series of studies centering on justice issues and their implication for policy and program development. They have been remarkable not only in content but also in their preparation. People from the health care field, theology, consulting firms, sponsoring groups, and academics were convened to produce "With Justice for All? The Ethics of Health Care Rationing," "No Place in the Market Place," and "A Time to Be Old a Time To Flourish." In addition, they were instrumental in facilitating the development of a commission that produced the influential "The Future of The Catholic Health Care Ministry." Each of these documents was endorsed by the board of the Association and gave rise to its remarkable CHA Leadership Task Force on National Health Policy Reform.

The Task Force developed a document, "Setting Relationships Right: A Working Proposal for Systematic Healthcare Reform." The proposal was in marked contrast to much of the material developed during the national debate on access to health care. It made its values explicit. It was centered on the notion that health care is a resource and that we must be good stewards of resources. Allocation must be in accord with human dignity and promote the common good. The document focused on the basic role of government in assuring decency for the poor. The proposal was specific and even had a realistic, well-founded price tag. CHA continues to be a player in the health care debate with a primary focus on the people who use health resources rather than on the institutions that are its members.

Cardinal Bernardin

This brief overview of the Church history on the issue of access to health care would be neither just nor timely without a brief allusion to the most widely respected member of the American Hierarchy, Joseph Cardinal Bernardin, Archbishop of Chicago. Cardinal Bernardin was in a position of leadership in the Church for the past quarter century, as the General Secretary of the United States Catholic Conference (USCC) and as President of the combined USCC and National Conference of Catholic Bishops. During his tenure he shepherded many of their formal statements on health through the sometimes arcane decision-making processes of the national body. Cardinal Bernardin lived with pancreatic cancer for some time. During this period he produced a pastoral letter on health for his own diocese, "A Sign of Hope," and delivered three seminal addresses to civic groups on Society and Health Care: "National Health Reform" (National Press Club, March 1994), "Making the Case for Not-For-Profit Health Care" (Harvard Business School Club of Chicago, January 1995), and at the national convention of the American Medical Association. The Cardinal personified the Church's commitment in the area of access to health care.

Conclusion

In our work on national health care reform we sought an organizing principle or theme.

One of the members suggested that we return to our roots and adopt the notion of a Year of Jubilee to which reference is made in Leviticus 25:1–55 and 27:14–16. This year would be a representation of a new vision for society, a profound reform that would reverse the wrongs of previous times, an expression of brazen hope for a reversal of former injustices and the restoration of the integrity of the people. It would be a time to erase divisions, a time to set relationships right.

When a society is just, prosperity and blessing result. As Isaiah said, "Justice will bring peace; right will produce calm and security." (Isa. 32:17)

References

1. United States Catholic Conference, I. Health and health care. (A pastoral letter of the American Catholic Bishop) November 1981:13.
2. Pope John XXIII. Pacem in terris. Encyclical letter. Washington, DC: Office for Publishing and Promotion Services, United States Catholic Conference, April 11, 1963. Article 11.
3. Kaufman CJ. Ministry and meaning: A religious history of Catholic health care in the United States. New York: The Crossroad Publishing Co., 1995:14–15.
4. Kaufman CJ. Ministry and meaning: A religious history of Catholic health care in the United States. New York: The Crossroad Publishing Co., 1995:18.
5. Kaufman CJ. Ministry and meaning: A religious history of Catholic health care in the United States. New York: The Crossroad Publishing Co., 1995:9.

Religious Perspectives on Access to Health Care:

A Jewish Perspective

Rabbi Harlan J. Wechsler

Abstract

There are three ethical ideas that undergird a Jewish approach to allocating scarce health care resources: the unique and absolute importance of every single human being, justice, and love. These three ideas are examined in light of the legal discussions that provide the context for health care decision making. Two classical sources are used, one that adjudicates the apportionment of a single flask of water between two men in the desert, and the other that creates an order of precedence when there are certain threatening situations. In the development of the legal tradition, several issues determine who receives care: ownership of resources, equitable distribution of resources, and effectiveness of treatment options. The obligation to provide access to medical care is reinforced by the values of *tzedakah* (justice) and love.

A Jewish perspective on access to health care grows out of three root ideas that are deeply embedded in the soil of Jewish literature and history.

Three Principles

The idea that every human being has infinite worth is first. In the language of the Bible man is created in the image of God. Each person therefore reflects the infinite value of God Himself.

Second, just as there are laws of nature, so is there a moral law. Part of the private agenda of individual human beings, as well as the public agenda of society, should be the pursuit of justice. Justice to the widow, the orphan, and the stranger. Justice to the rich and justice to the poor. "Justice, justice you shall pursue," the Bible says (1), and whether we are talking about the justice of courts or the obligation to leave the corners of the field for the poor, justice is a central concern.

Third is the understanding that, although God rules the world with justice and therefore that human life ought be moved by the constant search for it, God also is more than justice. He is a God of mercy. *Hesed,* in Hebrew, as its allied adjectives *rahum* (merciful) and *hanun* (gracious), are all words that connote a source of motivation for human action grounded first in God's love and then manifested in acts of human loving and caring.

I begin with these three theological ideas for I believe that most religions are best understood in light of the theological certainties that underlie the discussion of details. Indeed, Judaism is not a religion that develops as a result of the long-term elaboration of a theological principle. It is a religion of law. But law floats on a sea of ideas. And it is helpful to understand what that sea is like, to appreciate its tides and its currents, for ideally the captain will guide his ship in response to the sea on which it floats, never independently from it.

Rabbi Harlan J. Wechsler is Assistant Professor of Philosophy at Jewish Theological Seminary of America. Address correspondence to Rabbi Harlan J. Wechsler, Congregation Or Zarua, 1384 Lexington Avenue, New York, NY 10028.

Three ideas, then, the infinite worth of each human being, the pursuit of justice, and the demands of love, guide decision making in medicine, as in all areas of life.

Infinite Worth

To see the way in which "infinite worth" is embodied in life situations, I would like to focus on two cases from the period of the Talmud, each of which is about 1800 years old. Because they are so old, they are archaic in their formulation and, to our benefit, they have a long history of interpretation that follows them and that develops them from ancient days until our own. The first involves a dispute between two rabbis of the second century, one named Ben Petura and the other, the well known Rabbi Akiba.

> Two people were traveling on the road, and one of them has a flask of water. If both drink, they will both die; if one drinks he will arrive at the town. Ben Petura taught: "It is better that they both drink and die, and one of them not witness the death of his companion." Until Rabbi Akiba came and taught, "and your brother shall live with you" (Lev. 25:36). Your life takes precedence over the life of your brother. (2)

There is a limited resource, the flask of water, and it is in the hands of only one of the individuals. If both drink they will both die. If one drinks, he will be able to save himself. Now you might think that the conclusion of Rabbi Akiba is obvious, and of course that it would make sense to preserve a human life. But in the Talmud, few things are obvious. Although Rabbi Akiba gives a Scriptural source for his conclusion, the reasoning that drew him to it is not clear. To say nothing of Ben Petura. How could he have advocated a solution which would have allowed both to die rather than a solution that would have allowed one to live? His reasons, too, are absent in the Talmud.

Subsequent literature, however, tries to plumb the reasoning of both these scholars (3). There we find two principal interpretive traditions.

The first tradition sees the argument between the two rabbis based on the fact that one of the individuals has ownership of the flask of water. That fact of ownership means, according to Rabbi Akiba, that he has the right to take advantage of the resource to the detriment of his fellow. Property rights, therefore, can be exercised even when there is a possible moral imperative that would lead us to think that both ought to share (4).

Let us put this another way. Life is often unfair. Some end up with resources that others do not have. Some work harder than others. Some seek an education which will yield them a certain earning ability and others do not. Some families purchase insurance and others don't. These differences may be the result of circumstances beyond people's control, or they may be the result of circumstances that are well planned. Regardless, however, those differences enable different people to possess different resources which might be crucial either in the desert or in the emergency room one day.

Following this line of thinking, one of the commentators (5) suggests that if the flask of water were owned equally by both of them, then Rabbi Akiba would agree with Ben Petura that they both should drink and end up dying. The reason he suggests is compelling: How can you say that one man's blood is redder than his fellow's? (6).

Here you see our first principle of "infinite worth" exercising its effect. If all human beings are created in the image of God, then there is every reason to expect that all will have equal rights and that their precious lives will be equally valuable. Contingent circumstances, such as the fact that one person has access to a crucial resource in a calamitous situation, might make a difference. In this case, property rights are to be respected. Were that not the case, or if both owned the resource, then they would have equal rights to it.

Think for a moment about communal resources, those that we own in common. Some of them are natural resources, some of them are taxes. The apportionment of those commonly owned resources depends on the political process. But if we were convinced that the blood of each person was as red, how would we apportion those resources? By what goals would we demand our representatives to be guided to make those decisions?

There is yet another way of looking at the argument between Ben Petura and Rabbi Akiba (7). The difference between them may be understood as the difference between one person (Ben Petura) who feels that a limited resource should be extended as far as possible, "If both drink, at least they will both live another day or two . . . and perhaps by then water will be found" (7) and another (Rabbi Akiba), who believes that it is better to preserve one life rather than risk the likely chance that both of them will die.

Notice what is missing in this understanding of the case. There is no reference to ownership of the water. Ownership is, therefore, not the governing category. Indeed possession is relevant in deciding which of the two will drink. "[W]ere Ben Petura to agree with Rabbi Akiba's basic logic, that only one should drink, then he too might well agree that it should be the owner of the water who does the drinking. At issue between them is whether one drinks or two drink, not whether the owner drinks or they both drink." (3, p. 71)

It is the consequence of the allocation that is crucial. If there is a limited amount of medication, for example, Ben Petura would say that it should be divided equally. His reason might be: Who is to say that one person's blood is redder? And, indeed, prolonging a person's life with a scarce drug may enable him to live long enough so that more of the drug might become available, or maybe some effective cure will enable him to live. Rabbi Akiba, on the other hand, is concerned with the results. If one treatment is more effective than the other, you administer the treatment that works.

Let us see where we have come so far. We have seen a case in which there is a scarce resource and where access to it is necessarily limited. Based on our first principle, the infinite worth of human life, we have seen that such value may, in fact, be compromised by different factors, at least according to Rabbi Akiba. In both analyses, Ben Petura is consistent. There is no way to make decisions about allocating a scarce resource when it applies to a human life. Because every life is equally valuable, then it is better that both die than that one live. The higher principle is upheld, and that ennobles human life. Rabbi Akiba, on the other hand, sees reasons for mitigating circumstances, even when the infinite value of human lives is at stake. According to one view, it is the economic reality that is determinative. According to the other view, it is the practical result that makes all the difference.

Let me tell you where I am left at this point. I want to embrace Ben Petura, because he upholds the absolute importance of human life. I fear compromises. I am terrified by a slippery slope. Ben Petura is behind one of my recurring dreams (or is it a nightmare?). In this dream, we all become radicalized and hold out for the importance of every human life. In it we have masses of martyrs who will boycott our hospitals and say: I would rather die than take the place of a poor man. And many righteous people will die. Many rich and well-placed people will die. There will be mass hysteria and suddenly the public will say: Every human life is worthwhile! We cannot endure this horrendous situation. We will have to make health care accessible to all no matter what it costs—even if it means fewer computers in every home, fewer cars in every garage, fewer second homes.

That is only a dream, of course, a radical's nightmare and not something that is comfortable for me. I know, too, that the law follows Rabbi Akiba and that these compromises have to be made. Those with good jobs, those with good insurance, those with good bank accounts will have greater access. Those who will benefit most from a treatment should be treated first.

Who Takes Precedence?

This brings me to a totally different source that also affects the way in which we determine who should have access to health care, although it is a very odd source. Bear with me as we analyze it, for you will see how an ancient source is interpreted by subsequent commentators to reinforce the underlying principle of infinite human worth, contrary to what appears to be the original intent.

The issue is one of precedence. If two people both need a resource and only one can have it, which one gets it? The Mishnah (second century) discusses this by differentiating between those situations where one person takes precedence over another (8).

> A man takes precedence over a woman when it comes to saving a life and to restoring something lost. A woman takes precedence with regard to provision of clothes and to being redeemed from captivity. When both stand equal chances of being degraded, then the man takes precedence over the woman.
>
> A Kohen (priest) takes precedence over a Levite (a priest's assistant), a Levite over an Israelite (a member of one of the tribes of Israel), an Israelite over a *mamzer* (9), a *mamzer* to a *netin* (10), a *netin* to a convert, a convert to a free slave. When do we say this? When they are all equal. But if there were a scholar mamzer and an ignoramus High Priest, the scholarly mamzer would come first.

This is a curious Mishnah no doubt. Moshe Sokol (11) suggests that there are six principles of prioritization that lead to the order of precedence in the Mishnah.

1. *Capacity for performing* mitzvot (*religious obligations*). In particular this leads the man to take precedence over the woman in life-saving contexts, because he is obligated by more mitzvot.
2. *Relative degree of need:* This is behind the priorities of different forms of degradation. A woman, for example, is more likely to be sexually mistreated by her captors than is a man. Therefore she takes precedence. On the other hand, when they both are likely to be raped,

the man takes precedence because he is assumed to experience greater anguish caused by the abnormality of the act to be performed (sodomy).
3. *Social need* (12).
4. *Birth status.*
5. *Relation to the rescuer* (13).
6. *Scholarship,* which interestingly takes precedence over many other matters.

Shall we use this set of priorities to decide who has access to health care? We do see functioning hierarchies here, and if we need them in the arena of health care, might these serve at least as guidelines? Most certainly not. To begin with, they obviously conflict with our first principle. If everybody has equal infinite value, then how can we allow relatively arbitrary distinctions such as sex, family status and scholarship to upset our basic commitment? Of course, one might learn from this discussion in Horayot that I have led you astray and that such distinctions ought be made.

I have not led you astray, however. The subsequent legal history of this passage shows us that others have already done what we might like to do. Maimonides, in his code, omits the possibility that a man takes precedence over a woman when it comes to saving a life (14). One of the standard commentaries on the Shulhan Arukh, the sixteenth century Code of Jewish Law, limits the power of scholarship to determine who takes precedence by noting that in the author's day scholarship barely exists. Somewhat later, another authority suggests that the superiority of Kohen over Levite and so on has basically disappeared in his generation. Most important, new issues are raised, such as a capacity to maximize life. In keeping with the concept of prioritization, decisions about allocating scarce health resources could be made according to life-maximizing differences, as when one person has a greater likelihood of living than another, or when one person has a greater likelihood of reproducing than another. This may be a reason for selecting a young person over an old person, an older person in good health as opposed to an older person in poor health (3, pp. 85–86).

More contemporary analyses of this passage apply it to cases of allocating scarce resources in a rather astonishing way. Instead of taking the priorities in the Mishnah as law, they are abandoned. Instead, the notion of priority is accepted and extended to more comfortably modern schemes. For example, if one patient enters the emergency room before the other, then the first one who arrives has the right to treatment before the second one who arrives.

The specific priorities of the Mishnah are simply not applied in real cases. Rather, an internal transformation has taken place in the law, and decisions are made as a result of the application of norms of reason which reinforce the basic notions of the rights of each human being to be treated properly. Treating people equally remains a central priority. By favoring the first patient who arrives, for example, each patient is assured of equal treatment by virtue of an external, contingent factor which enables each one to be treated fairly.

To some extent the notion of priorities is extended to allow for Rabbi Akiba's approach: the effectiveness of a treatment can create precedence for a particular protocol. One might even seen this as a way of accepting the views of both Ben Petura and Rabbi Akiba. One wants to allocate equally. The other wants to set priorities. Now we have seen that these priorities are set with, among other things, an eye toward creating the greatest equality between human beings as well as the most effective use of limited resources.

I have discussed the first principle and its importance, and now I would like to address principles two and three: What does justice demand? What does love require?

Justice and Love

I have translated the Hebrew word *tzedakah* as justice. We usually think of it as charity, but this is really not the case. When, for example, the Torah requires that the corners of the field be left for the poor, that portion of the crop becomes theirs by right. A person who does not allow gleaners to do their gleaning, steals from them (15). In Biblical religion, wealth is a gift of God. The divine mandate requires that those who are the recipients give their due to the poor. It is the just due of the needy. *Tzedakah,* which has a clear overtone of righteousness, is justice being done.

Tzedakah requires a strong effort to meet the needs of those who are without resources. Thus the Talmud goes so far as to cite the Biblical requirement that the poor be given "sufficient for his lack," Deuteronomy 15:8) to teach that we are commanded to support the poor, not to enrich the poor. But his "lack" is to be construed broadly, "even a horse on which to ride and a servant to run in front of him." (16) According to the Shulhan Arukh,

> If it is appropriate to give him bread, they give him bread; if dough, they give him dough; . . . if to feed him, they

> feed him. If he is not married and wants to take a wife, they enable him to marry; they rent a house for him, and provide a bed and furnishings (17).

It is the community that is required to bear such burdens, and the agencies of the community that are responsible for collecting the needed funds and expediting their distribution to ensure adequate care for the poor.

The question to raise, of course, is whether medical care ought be part of that burden and whether there are any limits to it. In his study of *tzedakah* and health care (18), Aaron L. Mackler concludes that the requirement of providing health care for the poor goes back at least to the middle ages. "The financial needs of the sick have at least equal claim on communal resources as other requirements of *tzedakah*, and may have special priority." (19).

Note also that because the requirement to heal is a positive obligation for physicians, they are required to use their skills whether or not there is a certainty that they will be paid. However, physicians are not required to become poor themselves as a result. They are expected to spend a certain amount of their practice engaged in pro bono activities (18, p. 149). Rabbi Eliezer Waldenberg notes that when an individual cannot afford to pay for medical care, the court, on behalf of society, acquires the obligation for that person's healing. As Mackler concludes (18, p. 150), "If an individual cannot afford to pay for needed health care, the obligation to provide for such care devolves upon society as a whole. Society may legitimately choose any of a variety of ways to meet this responsibility, so long as the responsibility is met in every case of need."

Indeed, the community is not required to take on obligations which will impoverish the community at large. For example, when the Talmud discusses the redemption of captives, it places limits on the amount of money the community is required to pay. Although two opinions are entertained for this restriction, one cites the problem of overburdening the community. If the enemy knows that it will be able to receive from the community whatever it demands, then the price will continue to rise (20). Now I do not mean to imply that either physicians or hospitals bear any resemblance to captors who hold innocent people for ransom, but the very existence of a market where there is very great demand for the services will inevitably require some limits on the amounts of funds that will be expended for them. A downside of the community's involvement is that as the payer, it wants to control how much is paid.

This short discussion of the obligation of *tzedakah* leads us to the conclusion that there is a communal obligation to care for those who are in need, and within the Jewish tradition at least there is ample precedent for seeing this obligation met through mechanisms the society uses to care for the needy.

This is an issue of justice, not of mercy.

Where are we now? We have come to see that access to medical care is more than a good. A strong argument can be made for the fact that it is a requirement of justice. And while, in a premodern society, the presence of a horse or a servant might have provided the example of the outside limits that society had to reach toward in order to care for its indigent, how can a modern society do any less than consider medical care to be an essential service? Health care is as vital as the provision of water, police protection, and electricity even if we do not find this stated explicitly in ancient tomes.

There are limits to what we can pay. Society cannot afford whatever it wants. It cannot run up a deficit with impunity. But what does it want? That is the question—What does it want?

Were it not already sufficiently clear that there should be a goal to maximize access to health care for all human beings, then let me close by appealing to a value that goes beyond justice but can rarely be separated from it.

The Bible says that "You shall love your neighbor as yourself." (26). The same Rabbi Akiba who said that a man can drink his own flask of water comments that this verse of Scripture is "a great general principle of the Torah." Concerns for one's fellow go beyond the usual obligations. And just two verses preceding this in the Scriptures, the Torah says: "You shall not stand by while your neighbor life is in danger." (22) If a person is drowning in the river, then you are required to try and save him (23). How long a stretch of the imagination is it to say: If he cannot breathe, if he cannot see, if he cannot hear, if his body is ailing, try and save him. All of this requires access to health care.

Yes, you will tell me, if you have the water, then you can drink. Let me then paraphrase what Hillel said: We need to be concerned about ourselves. But if we are only concerned about ourselves, what are we? And if not now, when? (24)

References

1. Deuteronomy 16:20.
2. B. T. (Babylonian Talmud) Baba Metzia 62a.
   ". . .[*W*]*ith you*" implies that your life comes first (Rashi, 11th century commentator on the Talmud).

3. Sokol M. The allocation of scarce medical resources: A philosophical analysis of the Halakhic sources. AJS Review: The Journal of the Association for Jewish Studies 1990; 15(1):63–93.

   Sokol brings a philosophical perspective to the sources which sheds much new light upon them. Although my own conclusions differ somewhat from his, Sokol's collection and analysis of the classical sources is the starting point for all serious discussion of these issues.
4. Rabbi Chaim Ozer Grodzinski. Ahi'ezer. In: *Yoreh De'ah* 16 (Vilna, 1925), p. 35. Followed also by Rabbi Eliezer Waldenberg in his important book of medical responses, *Ziz Eliezer,* vol. 9, chap. 28. (see Sokol, p. 72.)
5. Rabbi Samuel Edels. *Hiddushei Aggadot* to the passage in Baba Metzia 62a (noted in his commentary as 62b!).
6. B. T. Pesahim 25b.

   "A man came before Rabah and said to him: The governor of my town has ordered me, 'Go and kill So-and-so; if not, I will kill you.' He (Rabah) answered him: 'Let him kill you rather than that you should commit murder; what reason do you see for thinking that your blood is redder? Perhaps his blood is redder.' "
7. Netziv, Rabbi Naftali Zvi Yehuda Berlin (19th century), *Ha'amek She'ela, She'ilta* 147:3. (See Sokol, p. 71.)
8. Mishnah Horayot 3:7–8.
9. An "illegitimate child," although not according to our modern understanding. Rather, a mamzer is a child who is the product of a union which is explicitly forbidden by the Torah. For example, the child of an adulterous relationship.
10. The child of Gibeonites who converted to Judaism during the days of Joshua (Joshua 9:17–27).
11. Sokol (1990), pp. 78–83. Much of his analysis is based on the classical medieval commentaries. It should be appreciated, therefore, that the Mishnah is silent as to its reasons. There is a rich vacuum, therefore, to be filled by speculation. I list them not in his order but in the order of their appearance in the Mishnah.
12. This is not clear in our Mishnah. The Talmud, in discussing this text, brings in additional people who take precedence. In those cases, the social value of an individual is determinative. [See Sokol (1990), p. 78.]
13. This is based not on our text but on B. T. Baba Metzia 71a: "When faced with a choice between members of my nation and idol worshipers, members of my nation take precedence; a poor person and a rich person, the poor person takes precedence; your poor (i.e., relatives) and the poor of your city, your poor take precedence; the poor of your city and the poor of another city, the poor of your city take precedence."
14. Maimonides, Mishneh Torah, Hilkhot Matnot Aniyim 8: 15. This is late twelfth century.
15. Mishnah Peah 5:6.
16. B. T. Ketubot 67b.
17. Yoreh Deah 250:1.
18. Mackler AL. Judaism, justice, and access to health care. Kennedy Institute of Ethics Journal 1991; June: 143–161.
19. Jakobowitz, *Jewish Medical Ethics,* New York: Bloch, 1975 106–109; and Shulhan Arukh, Yoreh Deah 249: 16. Cited in: Mackler AL, Judaism, justice, and access to health care. Kennedy Institute of Ethics Journal 1991; June: 143–161.
20. B. T. Gittin 45a.
21. Leviticus 19:18.
22. Leviticus 19:16.
23. B. T. Sanhedrin 73a.
24. Mishnah Avot 1:14.

Philosophic Perspectives on Access to Health Care:

Distributive Justice in Health Care

ALLEN BUCHANAN, PH.D.

THE AIM OF THIS ESSAY is to provide a basic conceptual framework that will advance the debate about distributive justice in health care beyond the often-repeated observation that there is a serious access problem. First, I will explain what it means to say that there is a moral right to health care, noting what the distinctive function of rights talk is in this context. Second, I will sketch very briefly two basic approaches to justifying the statement that there is a right to health care. Third, I will explain why, if there is a moral right to health care, it must be a limited right, and indicate what its limits are. Fourth, I will set out, more clearly and systematically than is usually done, the basic criteria we ought to apply in evaluating health care systems or proposals for health care reform from the standpoint of distributive justice. I will argue that distributive justice in health care includes more than establishing a right to health care for all. It also includes a fair distribution of the cost of establishing that right, a fair distribution of the burdens of rationing health care (given that rationing of some sort is inevitable), and a fair distribution of the fruits of publicly funded medical research.

What It Means to Say That There Is a Moral Right to Health Care

The phrase "the right to health care" can be understood as referring either to a legal right or a moral right. In this paper, our concern is with a moral right. There is no general legal right to health care in the United States. It is because there is no general legal right that the question of whether there is a moral right is so important. For if there is a moral right, then this can serve as a powerful justification for creating a legal right. Generally speaking, moral rights have an exceptionally strong claim to legal enforcement, if enforcement is required to establish them.

What does it mean to say that there is a moral right to health care, even if there is no legal right? It means three things. First, it means that there is a collective moral obligation, an obligation on the part of society as a whole, to ensure that everyone has access to some level of health care services. To the extent that government, at the highest level, is the proper agent for ensuring that important collective obligations are fulfilled, the federal government in our system has an obligation to see that the right to health care is secured.

Second, a moral right to health care means that the obligation is a very stringent one. In other words, the obligations that rights carry have exceptional moral force. They override what ordinarily would count as countervailing considerations, reasons for not doing what the obligation says that we are to do. In particular, in the case of obligations that are implied by rights, the mere fact that overriding the obligation would increase overall utility is not in itself a sufficient reason for overriding the obligation.

Third, to say that there is a moral right to health care is to say that access to health care is owed to those who have the right. This means that if we fail to fulfill our collective obligation, then we not only do something that is wrong, we

---

Joel Feinberg Professor of Philosophy, Grainger Professor of Business Ethics, Professor of the History of Medicine, Medical Ethics Program, University of Wisconsin, Madison, WI. Address correspondence to Professor Allen Buchanan, School of Business, 4289 Grainger Hall, University of Wisconsin at Madison, Madison, WI 53706-1490.

also wrong all those individuals who lack access to health care; we do them an injustice. In other words, as it is sometimes said, the posture of a person who has a right is not that of the supplicant, someone asking for a favor, or pleading for generosity. A right holder is someone who can make a valid claim on others (1). A right holder has moral standing to demand that to which he or she has a right. If one has a right to something, then it is not enough to say that if you got it this would be a good thing, as if your getting it were merely desirable, and in that sense optional. If you have a right to it, then you are entitled to it.

Given this understanding of what it is to say that there is a moral right to health care, it is easy to appreciate the distinctive function of rights talk in moral argument and in the discourse of political advocacy. Generally speaking, rights serve as especially powerful protection for what are assumed to be exceptionally important interests that individuals have. Statements about rights are declarations as to what the moral priorities are. They tell us that certain interests which people have warrant special protection. For example, to say that there is a right to freedom of expression is to declare that the interest individuals have in being free to express their thoughts is of such moral importance as to warrant protection, even though there are cases when greater social utility would be gained by suppressing expression.

Justifying the Statement That There Is a Right to Health Care

Understanding that rights are powerful protection for exceptionally important interests provides the key to understanding how statements about rights can be justified. We justify statements about rights by explaining why certain interests are of such moral importance that they deserve this special protection. In health care, we can articulate what these morally important interests are by reflecting on what makes health care so valuable. Health care is valuable because it prevents or delays unwanted death, reduces pain and suffering, restores or prevents the loss of important functions, and provides information that is useful in planning our futures (2, 3). Preserving our lives, avoiding pain and suffering, preserving important functions, being able to plan our futures—these are all fundamental interests for most if not all of us. The justification for the statement that there is a right to health care begins by clarifying how health care serves these fundamental interests.

Making the connection with these fundamental interests is not the entire justification, of course. It is also necessary to show that it is unreasonable to expect that individuals generally should be able to gain sufficient access to health care to be able to serve these fundamental interests exclusively by relying on their own private resources. If they were able to do this, then there would be little point to declaring that they are entitled to health care and that there is a collective obligation to ensure access to health care. Given that modern health care is extremely expensive, and given that health care needs are highly unpredictable, it is unreasonable to expect most individuals to be able to pay for health care out of their own pockets. Some sort of collective cost sharing is required. Private insurance for health care is a method of collective cost sharing; however, it cannot be reasonably expected to provide sufficient access to care for everyone, because those who are most in need of health care, those with especially high risk of ill health, will not be able to purchase affordable coverage, if they can find anyone to insure them at all. That is why we speak of a collective obligation, an obligation on the part of society as a whole.

At this point, justifications for the statement that there is a right to health care diverge toward two quite different paths, one leading to Utilitarianism (or, more generally, to consequentialism) and the other to what may loosely be called Kantian theories. For Utilitarianism, the only moral significance of ensuring that individuals have access to health care is that doing so maximizes overall utility (understood in different versions of Utilitarianism as satisfaction of preferences or pleasure). For Kantian theories, the individual as such, not preferences or pleasurable states of consciousness, is moral bedrock. Individuals are entitled to access to health care not because ensuring them access will maximize total utility, but because proper appreciation of the worth of individuals and the importance of health care to them warrants this entitlement.

Now, it may be that Utilitarianism can provide the basis for a right to health care for some. It is doubtful, however, that it can justify a universal right to health care—a right to health care for all, rather than just for some, or for most.

Consider Down syndrome. Individuals with this chromosomal disorder have a high incidence of cardiac and gastrointestinal defects, in addition to varying degrees of mental retardation. It might turn out that the way to maximize overall utility is to allow infants with Down syndrome to die of their congenital defects, especially if they were removed from their parents' sight at birth, before attachments could deepen. If this were the case, then Utilitarianism would not justify a right to health care for all.

Notice that we are not speaking of denying extremely expensive care or care that is costly or has doubtful efficacy. The point is that Utilitarianism would exclude some individuals from all health care entitlements if doing so could be shown to maximize overall utility, regardless of the benefit the individual would derive from treatment.

In what follows I will assume that what we are interested in is the idea of a moral right to health care that is universal. In other words, I will assume that distributive justice in health care requires access to care for all. Much is still obscure, however. We need to know (a) what counts as having access—that is, what is adequate access, to whatever everyone is entitled to have access to, and (b) to what is everyone to have adequate access.

Access without Undue Burdens

Distributive justice in health care requires not simply access—the ability to get services—but also that individuals not be subject to undue burdens in accessing services (3). Individuals can have access to health care in the sense that they can obtain services, yet there may be serious barriers to obtaining those services. The most obvious burdens are financial. If one must utterly bankrupt oneself to secure health care, then one may indeed have access, but not access without undue burdens. Similarly, if one can only obtain health care services after traveling extremely long distances, or waiting for very long periods of time, then one has access, but not access without undue burdens. In addition, if one must surmount barriers of racial, class, or gender prejudice, or experience stigma, in order to obtain services, then these too are undue burdens.

Access to What?

Even without settling on one systematic philosophical basis for the right to health care—for example, one particular version of Kantian theory—there are some things that can be said about the content of a right to health care. Most importantly, the right to health care cannot be an unlimited right. It cannot be the right of everyone to whatever health care services would be of any expected net benefit to the individual. In a word, the right to health care must accommodate the fact that there must be rationing of health care, that everyone will not be able to get every service that is of any expected net benefit. There are two reasons why the right to health care must be a limited right.

First, health care is not the only good in life. Given that resources are finite, if not absolutely, then at least relative to any time and place in which a society finds itself, we must consider what economists call the opportunity costs of providing health care for all. We must acknowledge that resources must be preserved for other social goods, such as education, housing, scientific research, the arts, and other cultural activities. If technological development continues, there is virtually no limit to how much we could spend on health care that offers a reasonable expectation of producing some benefit, if we disregard the other goods we would have to forego. No individual would find it rational to devote all of his resources to health care (or any other one good). Similarly, it would not be rational for society to devote all of its resources to this one good.

Second, there are limits as to what we owe others. Each of us has only one life to live, and it is appropriate that we give special priority, within limits, to our own projects and interests and to those of the persons with whom we are most closely connected. An unlimited right to health care, a commitment to provide all care that would be of any expected net benefit to everyone, would be a failure to recognize this fundamental point about the scope of our moral obligations to others. The right to health care is the right to an "adequate level" of care, not the right to all care that would be of any net benefit.

Just as it would be a mistake to assume that the right to health care is an unlimited right, it would also be an error to understand it as an egalitarian right, if this means that distributive justice in health care is incompatible with there being any differences at all in the availability of health care among individuals. Given that the right to health care is limited, then justice will be served if everyone has access, without undue burdens, to an adequate level of health care, even if some have access to care that exceeds the adequate level. In other words, given that the right to health care is a limited right, we cannot assume that equitable access to health care requires equal access to health care. Those who prefer more or different health care services than those included in the limited right to health care should be free to satisfy their preferences, if they have the resources to do so. The notion of an adequate level of care is that of a floor, not a ceiling (4).

So far, the adequate level of care, that to which everyone is entitled to have access, has only been characterized negatively; it is not a right to all care that would be of any net benefit, and it is not a strictly egalitarian right. As important as these negative characterizations are, we still need to know something about what is included in the right to health care, or at least we need some guidance as to how we are to go about filling out its content. Unfortunately, theories of distributive justice in health care have very little to say about the content of the right to health care.

Nevertheless, two points should be remembered. First, the adequate level of care for a given society must be specified relative to that society's resource base. This follows from the point, noted earlier, that whatever we include in the right to health care carries opportunity costs. In a poorer society, the problem of opportunity costs will generally be more severe, because there will be fewer resources to work with and fewer important needs will already have been met. Thus, the adequate level of care may look quite different in a country like Ethiopia, than in a country like the United States.

Second, at least in relatively wealthy countries, there are some clear candidates for inclusion in the adequate level of care. For example, in a country like ours, it is relatively uncontroversial to include the following types of items in the adequate level of care: at least two visits to a qualified practitioner during pregnancy, immunization against the more serious childhood infectious diseases, and screening for hypertension for all adults older than 40 years.

Once we attempt to go beyond such obvious candidates for inclusion in the adequate level of care, there will undoubtedly be disagreements about what ought to be included. In some cases, the same considerations that make health care valuable enough to give it the special protection of an entitlement will shed some light on the proper priorities. For example, if equal numbers of people would be affected regardless of the choice and one service would prevent unwanted deaths, whereas the other would merely relieve minor pains or provide information that would be of limited benefit for persons' efforts to plan their futures, then the former should be accorded priority. Similarly, health care interventions that would prevent the loss of major functions, such as vision, or independent locomotion, will be strong candidates for inclusion.

Nevertheless, there will be cases where difficult choices will have to be made in the absence of clear and objective criteria for assigning priorities. Here the best we can do will be to rely on reasonable and fair procedures for decision making. These will include input from medical experts (of the sort formulated at consensus conferences among specialty groups) and the workings of democratic political institutions.

Instead of dwelling on the problem of specifying what exactly the content of the right to health care is, I now want to try to enrich the debate about health care reform by expanding our understanding of the criteria by which we should evaluate health care policy proposals, from the standpoint of distributive justice.

So far, like most writers on distributive justice in health care, I have focused only on the right to health care—on the "who gets what?" question. I have argued that distributive justice in health care requires that everyone has access to an adequate level of care without undue burdens. This analysis of the right to health care gives us three criteria for evaluating proposals for health care reform. Would this proposal produce

1. universal access
2. to an adequate level of care
3. without undue burdens?

Distributive justice in health care requires more than the satisfaction of these criteria, however, because the right to health care is only one dimension of distributive justice in health care.

The Just Distribution of Costs

This fourth element, remarkably enough, is often neglected in philosophical accounts of the distributive justice in health care. By focusing on the right to health care, theorists have had almost nothing to say about the just distribution of the costs of ensuring access. They have discussed the "who gets what?" question, but not the "who pays for whom?" question.

I cannot offer a theory of the just distribution of the costs of ensuring equitable access here. At most I can only highlight the importance of the "who pays for whom?" question and suggest that this fourth criterion can yield substantive results in the evaluation of health care policy proposals.

Consider, for example, the ill-fated Clinton health care reform proposal. Many critics have complained that, in spite of the Administration's protestations, the plan's employer-mandated insurance is a thinly disguised tax on employers. This is no doubt true. The real issue, however, is not whether the employer mandate is a tax, but whether it is a fair tax. More precisely, the question is whether the whole financing system, of which the employer mandate would be one element, would achieve a fair distribution of the costs of ensuring universal access (or rather the approximation to universal access that the Clinton plan was designed to deliver).

The point is that one cannot even answer the question of whether the employer mandate is a fair tax without seeing how it is to function in the entire, complex financing scheme of the plan. Certain elements of that scheme are suspect, however, from the standpoint of fairness. The most obvious instance is the plan's insistence on a flat premium (for the standard benefit package) for everyone. What this means is that the poorly paid janitor pays the same dollar amount for the standard benefit package as the richest CEO. This feature of the financing scheme is clearly regressive: instead of requiring the better off to pay a larger proportion of the costs of securing access for all, it imposes a greater proportional burden on the worse off. Another regressive feature of the Clinton plan, and of every other plan forwarded to oppose it, is the preservation of the tax exemption for the employer's contribution to employees' insurance premiums. This tax exemption is in effect a massive subsidy for the middle and upper income classes. It is worth noting that the total value of this government subsidy for the better off considerably exceeds the total federal funding of the Medicaid program for the poor.

Once it is acknowledged that some redistribution of wealth is needed to secure universal access without undue burdens, it seems obvious that the better off generally should bear a greater share of the costs. But if this is so, then a policy proposal that has these sorts of regressive features is immediately suspect from the standpoint of distributive justice. This is not to say, of course, that I, or anyone, at present has a good theory of how great a share of the costs the better off should bear.

Additional Criteria

So far I have sketched a set of familiar criteria for evaluating the justice of health care systems and policy proposals and urged that they be supplemented by requiring that the costs of securing access for all be fairly distributed. The expanded list of criteria for distributive justice in health care reads as follows:

1. There is to be universal access
2. to an adequate level of care
3. without undue burdens in obtaining services
4. achieved through a fair distribution of costs.

I now wish to suggest two additional criteria that are extremely important, yet rarely mentioned, much less systematically applied, in the evaluation of health care systems or proposals for reform. The first is that the system by which adequate access for all is achieved should be one in which the burdens of rationing are distributed fairly. The second is that the system should ensure that the fruits of publicly funded medical research are distributed fairly.

The significance of each of these additional criteria can be illustrated with examples. Consider first the requirement that the burdens of rationing be fairly distributed. I already noted that rationing is inevitable insofar as the right to health care itself must be a limited right; a right to an adequate level of care, rather than to all care that would be of any net benefit. In that sense, deciding what is included in the adequate level of care to which all are entitled is already a rationing decision. If the process of prioritizing health care services that results in determining what is included in the adequate level of care is biased, then the distribution of the burdens of rationing will not be fair.

But even if there is no bias in determining what services are included in the adequate level of care, there can still be unfairness of a more subtle, less obvious sort. For each of the various services that are included in the adequate level of care, there will always be choices as to the timing, intensity, and quality of services to be provided. The impetus for these more subtle rationing decisions will come from two main sources. On the one hand, as technology and knowledge advance, there will be pressure to expand the list of services included in the adequate level. If adequate additional funding to cover new services is not available, they will have to be financed partly out of cost savings in the provision of existing services, if cuts in existing services are to be avoided. How much it costs to provide services can be influenced by the timing, intensity, and quality of their provision. On the other hand, as the population ages and the number of tax-contributing persons in the work force decreases, there will be fewer dollars to pay for the adequate level of care. To avoid cutting existing services it will be necessary to economize on their provision through manipulating the timing, intensity, and quality of their provision. Some ways of doing this will be fairer than others.

When it comes to rationing decisions in the provision of the adequate level of care, there are two distinct sources of unfairness to be guarded against: unfair rationing principles and unfair application of fair principles. Unfairness of the second type, though often difficult to detect and to remedy, is readily understood. If the application of fair principles is distorted by biases toward women or ethnic or racial groups, it is obvious that an injustice has been done.

It is quite another matter, however, to know whether a rationing principle is itself unfair. The difficulty here is not that we have no shared intuitions about what fair rationing principles are, but that we have too many intuitions and that they are in apparent conflict. For example, should an extraordinarily expensive new cancer drug be given only to those patients who have the best chance of a beneficial outcome or should it be distributed by lottery among all who might benefit to some extent from it? The conflict here, which is familiar in the literature on rationing organs but is of much more general relevance, is between two rationing principles, each of which enjoys some intuitive appeal. The one principle says to distribute scarce resources so as to maximize expected benefit (roughly, to do the most good). The other principle says to give everyone who might benefit an equal chance of receiving the resources. Which principle should have priority—greatest benefit or equal chances? Sadly, theories of distributive justice presently have very little if anything systematic or even coherent to say about how to balance such conflicting rationing principles.

Consider now a fifth criterion for evaluating health care systems and proposals for reform: that the fruits of publicly funded research should be fairly distributed. To take only one example among many, consider the advances in the detection, prevention, and treatment of genetic diseases that are expected to result from the infusion of public funds into the Human Genome Project. The chief justification for public funding for the Human Genome Project was that the public—the public as a whole, not just those able to pay for genetic services—would benefit from the fruits of this research. In a just system, this promise would be kept. A system in which public funds that are supposed to benefit all do not do so is criticizable on grounds of justice. If, in addition, some of the knowledge that emerges from the Human Genome Project not only fails to benefit some citizens, but in fact is used by insurers, employers, or the government to harm them, then the injustice is compounded.

Conclusions

This brief survey of justice and rights in health care has produced the following list of criteria for evaluating health care systems and proposals for reforming them.

1. There is to be universal access
2. to an adequate level of care
3. without undue burdens in obtaining care
4. achieved through a fair distribution of the costs of providing universal access
5. with a fair distribution of the burdens of rationing
6. with a fair distribution of the benefits of publicly funded research, at least so far as the justification for public funding is that the public as a whole is to benefit.

So far, theorists of justice have focused almost exclusively on the first two criteria, with some recognition of the importance of the third. Neither theories of justice nor the public debate have reflected a full appreciation of the significance of the last three criteria.

References

1. Feinberg J. The nature and value of rights. In: Moral problems in medicine, Gorovitz S. et al., eds. Englewood Cliffs, NJ: 1976:454–67.
2. Daniels N. Just health care. Cambridge, England: Cambridge University, 1985.

   Daniels has emphasized the importance of preventing loss of or restoring functioning as a goal of health care, and has stressed the importance of normal species functioning for individual's opportunities.
3. Securing access to health care, vol. 1, Report, President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Washington, DC: Government Printing Office, 1982:11–47.

   Provides an account of what makes health care valuable.
4. Buchanan A. The right to a 'decent minimum' of health care. Philos Public Affairs 1983; 13(1):55–78.

   An examination of various arguments for the right to health care as the right to an adequate level of care.

Philosophic Perspectives on Access to Health Care

Putting the Care into Health Care

Joram Graf Haber, J.D., Ph.D.

"Justice is a cold jealous virtue."
—David Hume

How should we think about social inequalities in the health care setting? Are they cases of injustice that need to be remedied? Are they examples of misfortune that call for compassion? Perhaps the answer lies somewhere in between.

Charity

Those who are "fortunate" enough to meet the definition of poverty stipulated by their state-run Medicaid programs are allowed access to health care through entitlement programs. This is a mixed blessing. It is good inasmuch as those meeting the definition have access to health care and are not without protection from illness. It is bad inasmuch as states reimburse only a fraction of physicians' rates, and few private practitioners are willing to treat Medicaid patients. With the exception of some uncommonly devoted physicians, those who accept Medicaid patients are often poorly qualified and offer substandard care in large, impersonal settings. Hospitals that deal with predominately Medicaid patients are notoriously understaffed and undersupplied, and teaching hospitals that accept Medicaid patients are often located in inner cities where overworked interns and residents provide suboptimal care.

Entitlement programs are bad for another reason. In American society, health care is a privilege. The Constitution neither requires nor prohibits it. This means that it is not unconstitutional for a state to withdraw or withhold access to health care programs. This is not to say that once a state allows such a program, it can run that program arbitrarily. The Fourteenth Amendment requires that citizens be accorded equal protection under whatever laws are constitutionally enacted, without specifying which laws should be enacted. If Congress or a locality provides funds for health care, they must do so in ways that meet what the Supreme Court sees as constitutional requirements. Health care in the form of Medicaid exists as a charitable institution as does the Medicare system on the federal level. Each is a welfare benefit that government confers on its citizens which is available to all who are eligible to apply.

A Right to Health Care

So what is wrong with that? Aside from the problem of inferior care, the problem is the program's grounding. Insisting that a right to health care exists, some moralists claim that a health care system that exists as a matter of governmental charity is unjust because it merely tolerates or allows that to which we have a right. Think of how abhorrent it would be if the state let us live on account of its beneficence, or "allowed" us to live in accordance with our individual conceptions of the Good. Although we would be happy to be alive and to act autonomously, we would insist that our lives and our liberty are things which we possess as matters of right. Granting only a privilege to that which we possess as a matter of right is unjust, even if we benefit from what we are granted. Consequently, even if health care for the poor as presently conceived were perfectly adequate, its moral basis would still be in question.

The "privilege" of receiving Medicaid also applies only to those who are below the poverty line. Those who rise above the line, but not so far above as to be able to purchase adequate health care, have no such privilege. To them, American society answers by allowing the purchase of health care in the free marketplace. But health care in

---

Address correspondence to Joram Graf Haber, J.D., Ph.D., Assistant Professor of Philosophy, Bergen Community College, 400 Paramus Road, Paramus, NJ 07652-1595.

the free marketplace is costly. Where its cost is affordable, its quality is limited by the interests of Health Maintenance Organizations which are driven primarily by considerations of profit.

Moralists who are critical of health care as charity argue that health care should be assured as a matter of right. Much of the work in this area has therefore tried to show the basis of this right as well as its scope. Rejecting charity as well as laissez faire allocating structures, these moralists locate the source of this right in a preferred theory of distributive justice. Allen Buchanan (1) favors a decent minimum conception according to which each person is entitled, by right, to a decent minimum of health care. The right to health care would be determined on the basis of need which society would then be obligated to provide. Better services, in this view, would be available for purchase at personal expense by those able and willing to do so.

John Rawls (2) argues for a similar view utilizing the mechanism of the social contract. In Rawls' view, no rational and self-interested contractor operating behind a veil of ignorance would agree to a social contract that enables the fortunate to hang on to what they have but fails to provide a decent life for those who are poor and sick. This leads Rawls to argue for a decent floor below which no one should fall while allowing for better services for those who can afford them under conditions of equal opportunity.

Robert Veatch (3) proposes a system of health care based on an individual's health care needs by using the yardstick of "equal right to health care." In Veatch's view, "people have a right to needed health care to provide an opportunity for a level of health equal to the health of other people." Against Buchanan and Rawls, Veatch argues for a health care delivery system with one class of services instead of the two-tiered system Buchanan and Rawls favor.

Justice and Rights

Regardless of the differences among them, Buchanan, Rawls, and Veatch generally approach the problem of health care allocation by emphasizing justice and rights. Another approach has gained momentum in recent years, however. Harvard psychologist Carol Gilligan (4) has offered an ethic of care to rival the traditional ethic of justice. This new approach is advocated by such moralists as Annette Baier (5), Lawrence Blum (6), Virginia Held (7), Michael Stocker (8), Laurence Thomas (9), and others. It recognizes that although justice may be the "first virtue of social institutions," as Rawls had put it, it is not the only virtue. Friends of the care ethic usually argue that, for justice to deliver its unquestioned value, other virtues are needed as well. Care is advanced as the most plausible choice. Because health care historically has been viewed as a matter of charity, and care is the contemporary descendant of charity, a discussion of charity in the context of health care cries out for a care-based approach.

Care and Ethics

What is an ethic of care? How does it differ from an ethic of justice? How might a care ethic respond to the issue of access to health care? The questions are hard for many reasons, not the least of which is that the care ethic is not a monolith. The care ethic is a cluster of concerns centering around the view that care is a cardinal virtue of morality. Beyond that, advocates of the care ethic don't always agree. Most advocates construe care as an ethic that applies mainly in the domain of personal relations, or one-to-one encounters in which the cared-for person is a specific individual. Fewer advocates have made moves toward applying a standard of care in the more public and impersonal domains of social policy. My aim in this paper is to see how such an ethic might speak to the issue of health care policy. I will do this by delineating some general themes of the care ethic, and then seeing how we might use that ethic to arrive at some answers for the allocation of health care.*

An ethic of care has two components. The first one addresses what is wrong with an ethic that takes justice and rights to be primary. The second component addresses ways in which a care ethic can correct what is wrong with the rights approach. As we will see, the critical and constructive approaches are intertwined.

The main target of the care ethic is social contract theories, from Hobbes and Locke to Rousseau, Kant, and, most recently, Rawls. For these theorists, the social contract is advocated as representing what we might all agree to if we were in a state of nature and able to freely choose the principles on which to establish social institutions. From the care-ethic perspective, social contract theory is marred by the tacit premise that the individuals entering into such contracts are economically (and psychologically) self-sufficient.

---

*In delineating the care ethic, I am drawing heavily on the work of Annette Baier whose work clearly addresses this point. See Reference 5.

Historically, social contract theory has presupposed a model whereby contractors were independent farmers or craftsmen who, if they had no property already, could acquire property and become self-sufficient. Locke, for instance, argued that the way to acquire property was to mix one's labor with unowned land. In answer to the question, "What if there is not enough unowned land to go around?," Locke answered, "Go to America where land is plentiful!" Social contract theorists historically have favored a distribution pattern that would let people enjoy what they already owned and allow them to pursue their private interests. This vision led to the Western liberal democratic systems of rights and liberties in which taking away from someone what was rightfully theirs—life, liberty, property—was recognized as wrong, whereas the failure to respond to the needs of those who had no property and were unable to acquire any was not treated as wrong (or very wrong).* Between the haves and have-nots, the rights approach historically has favored the haves to the detriment of the have-nots.

Favoring the haves would not be a problem if those who have not were able to acquire what they lacked. But many can not. Although in Locke's time people were able to fend for themselves and secure primary goods, today this is no longer true. Almost everyone today works for a living and is forced by economic necessity to do business with corporate enterprises. They can no more escape the power and control of corporate enterprises than they can escape the government. They sell their labor and buy their products, while corporate enterprises pursue their profit-driven interests. It will not do, then, to say to such people: Go fend for yourselves! Such an attitude is heartless, cold, and irresponsible. And it is no less heartless, cold, and irresponsible to let those who have not fend for themselves hoping that the charitable impulses of others will fill in the void. (For a fuller discussion of these points, see Reference 10.)

This is the problem with contract theory: it tacitly favors the rich and powerful. If social contractors seriously considered that they themselves might be destitute and powerless the way many of us are in contemporary America, they would never agree to a social contract that enables the fortunate to hang on to what they have but fails to provide a decent life for those unable to be self-sufficient. They would never cavalierly leave the defenseless to their own devices or to the charitable whims of the rich and powerful.

Against Locke, Rawls' theory of justice takes seriously the possibility of finding ourselves losers in the distribution of goods. This is why Rawls insists that the contract be made from a position of ignorance where the contractors don't know if they will be haves or have-nots. That reason argues for a minimum floor.

The problem with Rawls' views from the care perspective is that they are more about emphasis than they are about substance. In Rawls' theory, losers in the natural and social lotteries are still entitled to a minimally decent life. We therefore need not concern ourselves with the loser's lot because Rawls' theory of justice will not let them fall (or fall very far). But this, too, is cold, say care-ethic advocates, because it views society as consisting of detached, independent, and self-interested individuals who freely bargain for interdependence and cooperation. The care ethic, by contrast, sees a society made up of interdependent individuals who are inherently connected by their common humanity. As feminists are fond of reminding us, we start out as children, dependent on caretakers, and remain interdependent throughout our lives.

Let us consider this point from a Kantian perspective. In Kant's version of a society ordered by justice, members respect equal rights to such liberal goods as due process, equal opportunity, free speech, and religious worship. The problem with Kant's society from the care perspective is that none of these goods does much to ensure that the people who have them will have any more than minimal relationships with others. What results is alienation, apathy, despair, and meaninglessness.

The care-ethic criticism of the rights and justice approach, then, is largely a criticism of the individualism that has typified Western liberal social philosophy. It is a criticism of the desirability of each person pursuing her own good in her own way, constrained only by a minimal machinery that enforces contracts and protects individuals from outside interference. Defenders of the care ethic point out that noninterference, especially for the powerless but also for the indigent and infirm, can be tantamount to neglect. When it does not amount to neglect, it causes isolation and alienation.

How would a defender of the rights ethic respond to this critique? One response would be to point out that the rights approach is not inconsistent with the care approach. Supporters of the rights approach might say, "Let whoever wants to cultivate this more demanding version of morality do so once we have agreed on a minimum conception of justice and rights." Beauchamp and Childress (11) respond this way, as does Engelhardt (12). (See Reference 13 for an analysis of this response.) Supporters of the care ethic are not appeased. While admitting that the rights approach is not inconsistent with the care approach, supporters of the care approach point out that a rights approach could encourage exploitation and free-ridership. Recall the point about contract theory, and how it tends to lock in the status quo that benefits the rich.

---

*For this reason, the doing/allowing distinction might not be as morally neutral as one might expect.

Defenders of the care ethic remind us how the rights approach historically has oppressed those whom the right holders depended on to do the work the right holders themselves did not want to do. Domestic work, for example, was left to women and slaves whereas the right holders pursued their preferred interests. In the health care profession, physicians have historically been off treating patients, but the job of caring was left to nurses. Emphasizing minimal requirements of rights and justice but encouraging others to care for the needy may work to oppress those who are caring while providing free rides for the right holders.

Beyond concern over exploitation, defenders of the care ethic point out how a rights approach, particularly a contract approach, tends to regulate relations among equals and turn aside relations among unequals such as between men and women, the rich and the poor, the healthy and the sick. Often, the rights view corrects this disparity by promoting the disadvantaged to give the appearance of equality. The indigent and infirm, for instance, are treated as extensions of their more potent selves so that their rights are seen as the rights of equals. Witness, for instance, how the mentally ill are often referred to as health care consumers even when their capacities are clearly impaired. Although this pretense of equality sometimes leads to desirable protection, it also conceals the relationships that should prevail among persons in unequal positions of power.

The claim is that if we honestly admitted that we are all more or less powerful, more or less independent, more or less healthy, we might take a more direct approach to issues concerning the design of institutions, for example, hospitals, that structure relations between unequals. This is why defenders of the care ethic refuse to accept liberal rules as setting a minimal floor. They see the rules as doing little to protect the infirm and indigent against neglect, and doing little to ensure the kind of moral education that will shape people to accommodate an ethic of care. As Annette Baier has stated, caring for the less fortunate members of society is vital to our future success, and we cannot view our concern for people as an optional charity left for those who have the taste for it (5, pp. 53–54).

Yet another problem the care ethic has with the rights approach is a perceived obsession with rationalism. This is itself perceived as an outgrowth of an obsession with autonomy. The rights approach views contract as the paradigm source of moral obligation and contractors as rational and autonomous moral agents. It follows from this that a person's passions are not a problem as long as they are subject to the will of the agent. Kant is notorious for taking this view. He regarded the passions as morally irrelevant and needing management and control. But consider how people are not good parents if they only control their irritation and fail to care for their children. Consider how people are not good friends if they perform acts of friendship solely out of duty, but fail also to love their friends. If we remind ourselves that family is no less important an institution than the state, and remind ourselves how vital friendship is for human flourishing, then we may glean from these reminders some insights into how our social institutions should be ordered. The most important of these insights is a concern for virtue, the virtue of care but other virtues as well, alongside and equal to a concern for justice.

Universal Health Care

In 1992, Bill Clinton was elected President of the United States partly because of his commitment to provide universal health care coverage. Apparently, Americans exhibited the commitment to this idea and then failed to exhibit the will to match it. To the extent that this is true, the answer to the problem of health care access lies in the will and desire to make it work. But we cannot effect an adequate solution unless we take on other people's problems as our own instead of treating them as so many problems in a game of chess. Thus, although justice speaks of people's health care needs, situations, and welfare, care speaks of *wanting* good for other people. We need to become the kind of people for whom caring about others is a virtue. We need to become the kind of people for whom failing to provide adequate health care can evince an absence of caring despite a sincere belief to the contrary.

As defenders of the care ethic argue, caring about others cannot be cultivated without close cooperation from others. Respect for rights and justice is too compatible with our laissez-faire everyday ethic that makes no demands on what we may do with our material resources, and that does not require us to benefit others (14, 15). We need a more demanding version of ethics, one that recognizes that the distinction between doing wrong and allowing evil might itself be a reflection of an impoverished ethic. For this reason, we might do well to concern ourselves with an approach to ethics which emphasizes virtue and care as much as it emphasizes rights and justice. (Throughout this paper I have treated care as a virtue and have glossed over distinctions some theorists make between a care ethic and a virtue ethic.)

Developing Virtue

To begin, we might consider Aristotle's theory of moral development. Aristotle had no compunction about teaching children moral behavior. He thought that proper upbringing was needed for adults to take pleasure in doing what virtue requires and to suffer pain when practicing vice. By rewarding good conduct and punishing bad, Aristotle was convinced that the child's character would be molded into what it ought to become. In his view, a successful moral education habituates a person to live a life in which appropriate emotional and cognitive capacities are developed.

We become virtuous, said Aristotle, by performing virtuous acts until they become second nature. We acquire the virtue of charity, for instance, by being exposed to situations calling for compassion, acting appropriately, and having such conduct rewarded and reinforced. In this way we grow up having the disposition to exhibit the right amount of compassion when faced with situations calling for it. Just as we become fit by doing things that require physical strength, we become good by behaving virtuously. The desired effect of moral education is to habituate children to feel displeased by what is wrong, and delighted by what is right. Later, when children develop their ability to reason and acquire an understanding of the social and political world of adults, they can analyze what they learned and modify their judgments where needed.

Of course, we need more from a care-based ethic than the platitude that says we should care about other human beings, the infirm and indigent in the context of health care. We need to specify the manner in which care and justice work with each other. We need to ask such questions as whether and to what extent justice and care are compatible; whether one has priority in cases of conflict; whether justice and care apply to the same or different domains. These are questions that care-ethic advocates have already begun to address.

Conclusion

I submit that the rights approach is well meaning and acceptable as far as its goes, but it does not go far enough. Also, it is obvious that care is a virtue that is in short supply. As the fate of the Clinton plan shows us, we cannot rely on justice and rights to guarantee that the needy will have the kind of health care coverage that proponents of the rights approach endorse. The failure of that plan suggests that the well-meaning people of our society have not cared enough about the concerns to which they nominally subscribe. The prevailing pattern of a laissez-faire morality, even with a minimum floor, will not suffice. Without the kind of charitable dispositions that the care ethic shows us to be essential, universal access to health care will not be achieved. From the perspective of the care ethic, the rights view is poor medicine for the social inequalities that ail us.

References

1. Buchanan AE. The right to a decent minimum of health care. Philos Public Affairs 1984; 13(1).
2. Rawls J. A theory of justice. Cambridge, MA: Harvard University Press, 1971.
3. Veatch RM. A theory of medical ethics. New York: Basic Books, 1981.
4. Gilligan C. In a different voice. Cambridge, MA: Harvard University Press, 1982.
5. Baier A. The need for more than justice. In: Hanen M, Neilsen K, eds. Science, morality, and feminist theory. Calgary: University of Calgary Press, 1987.
6. Blum L. Friendship, altruism, and morality. London: Routledge & Kegan Paul, 1980.
7. Held V, ed. Justice and care: Essential readings in feminist ethics. Boulder CO: Westview Press, 1995.
8. Stocker M. The schizophrenia of modern ethical theories. J Philos 1976; 73(14):453–466.
9. Thomas LM. Love and morality. In: Fetzer JH, ed. Sociobiology and epistemology. Netherlands: Kluwer Academic Publishers, 1985.
10. Held V. Rights and goods: Justifying social action. Chicago, IL: University of Chicago Press, 1984.
11. Beauchamp T, Childress J. Principles of biomedical ethics. New York: Oxford University Press, 1994.
12. Engelhardt HT. The foundation of bioethics. New York: Oxford University Press, 1996.
13. Donchin A. Reworking autonomy: Toward a feminist perspective. Camb Q Healthc Ethics 1995; 4(1):44–55.
14. Sabini J, Silver M. The moralities of everyday life. New York: Oxford University Press, 1982.
15. Thomas LM. Vessels of evil: American slavery and the Holocaust. Philadelphia, PA: Temple University Press, 1993: 45–56.

Public Policy

The Health Care Juggling Act: Balancing Universal Access, Cost Containment, and Quality Improvement

Mark R. Chassin, M.D., M.P.P., M.P.H.

In the health care reform debate of the early 1990s, universal access to health care was a generally accepted goal. The central question that drove the discussion was how to pay for it. Proponents of universal access were unable to formulate an answer to this question that did not rely on increased taxation. More than any other factor, this failure explains the demise of health care reform.

At the outset of the debate, few if any dissented from the proposition that universal access to care should be a major objective of the reform effort. When it became clear that agreement on financing could not be achieved, differences of opinion began to emerge. Initially, the dissenters did not deny the importance of universal access to health care. Rather, they tried to change its meaning. Some argued that all Americans already had access to health care, because when they got sick they could go to hospital emergency departments. Others argued that simple tinkering with the market for health insurance would make access to health insurance available to all (albeit at extremely high prices for some) and that we should be satisfied with achieving universal access to health insurance.

Universal Access

From the perspective of public policy, we should be clear about what we mean by universal access to health care, about what arguments justify supporting this goal, and whether there are any ways to achieve it without adding more public funds to the health care system. This paper will discuss each of these questions in turn.

One definition of universal access to care could be equal access to care for all, a national health care system which is financed entirely by public funds and from which all citizens would be equally able to receive services, solely on the basis of medical need. The Canadian health system comes very close to operating in this manner. In the United States, however, equity is not a highly prized value. It is unlikely that more than a small minority of Americans would support equal access as the fundamental principle for reforming health care delivery. This view was reinforced by the meager support garnered by advocates for a single-payer approach to financing health care during the health care reform debate, which culminated in the resounding defeat it suffered when put to a vote in California in November 1994.

A more politically supportable model for defining universal access to care may be analogous to the approach we have taken to public education. We believe that all Americans should be eligible to receive publicly funded education through high school. In addition, we have invested substantial public funds to create state college and university systems that offer college and graduate education at substantially lower cost than private educational institutions. The vast majority of Americans receive most of their education in publicly funded schools. We do not, however, prohibit wealthier citizens from purchasing education privately.

But what is the argument for supporting the delivery of such an extensive array of health services through a publicly funded mechanism? Why

---

Address reprint requests to Mark R. Chassin, M.D., Box 1077, Department of Health Policy, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029.

should we treat health care the same way we treat education? One of the most important public policy arguments in favor of public education is that an educated public and an educated work force are such desirable public goods that they are worth expending large sums to create. I believe that an analogous argument applies to health care. A healthy work force is a more productive one, and a productive work force is integral to a healthy economy. This relationship is understood by business management and explains, at least in part, why health insurance benefits are provided nearly universally by businesses to their most valuable employees.

Unfortunately, the strains of competition block the efforts of even the most well-meaning employers when the standard in a particular industry is not to provide health insurance. The increased cost of providing health insurance when one's competitors do not is a powerful force preventing employers from doing so. This is especially true in the service industries, which demonstrate the lowest proportion of providing health insurance benefits of any class of business.

By similar reasoning, one can make a strong argument in favor of universal access to health care based on the principles on which our country was founded. The Declaration of Independence states:

> We hold these truths to be self-evident, that all men are created equal, that they are endowed by their Creator with certain unalienable rights, that among them are Life, Liberty, and the pursuit of Happiness, that to secure these rights, Governments are instituted among men.

It is difficult to conceive of anything more integral to the achievement of these three goals than good health. Does it not follow that, as a nation, we have a vital interest in doing as much as we can to ensure good health for all our citizens? Even if one believes that only equal opportunity, as opposed to equality of outcome, is guaranteed by the Constitution, what could be more inimical to an individual's ability to pursue economic or social success than poor health?

In this regard, the United States does not fare well in international comparisons. In the early part of the health reform debate, many observers noted that among developed nations, only South Africa and the United States had failed to provide universal access to health care. With the election of Nelson Mandela in 1994, South Africa has taken the first steps toward that goal, beginning with women and children. The United States now stands alone in this failure.

Having argued that universal access to health care makes good public policy sense and that universal access does not require equality of access, let us clarify several other implications of this concept. Universal access to care does not require that government operate the health care system, either by employing physicians or by owning hospitals. Nor does it require the elimination of diversity in the system of delivery; managed care plans of various sorts could easily continue to operate, private insurance companies could continue to provide administrative services (as they have done for more than 30 years in the Medicare program), and individual consumers could continue to make choices among alternative health plans.

To be meaningful, however, universal access does require more than the ability to present oneself to a hospital emergency department when acute illness strikes. This kind of episodic, discontinuous care cannot be considered adequate by any reasonable standard. Universal access to care also requires more than a market for health insurance that provides a wide array of policies, many of which are available to the people who need them the most (those with chronic illnesses) only at an exorbitant cost. To be at all meaningful or effective in improving health, universal access to care must make effective preventive and therapeutic health services available. I would argue further that this availability should not be impeded by significant financial or geographic barriers. It should also include as a basic principle access to high-quality primary care as well as appropriate specialty care.

Defining universal access in this manner leaves little doubt that achieving it will increase the costs of care for a significant and growing segment of the U.S. population. Well over 40 million of our fellow citizens lack health insurance. The evidence is compelling that lack of insurance results in markedly lower levels of health service use and poorer health. This underuse is particularly severe when one considers the most sophisticated kinds of health care, such as cardiac surgery and organ transplantation. For example, in New York State nonelderly people living in the most affluent areas undergo coronary bypass surgery 95% more often than those who live in the poorest regions (1). In California, the comparable figure is 30% more often. In Canada, with its universal access health care system, the poor are no less likely to receive this intervention than the rich. This observation raises another important implication of universal access to health care.

Too Many Specialists

By nearly all estimates, the physician work force in the United States consists of too many specialists (2). Some observers suggest that if present trends toward the increasing dominance of managed care continue, we may have as many as 150,000 too many specialists. In regions with particularly intense competition among managed care plans, such as California, specialists are retiring in their 50s and specialty training program graduates cannot find jobs. The reasons are not hard to understand. Nationally, we have 114 practicing specialty physicians for every 100,000 citizens (3). The Kaiser-Permanente system of managed care employs only 58 such physicians for every 100,000 of its enrollees, and Kaiser is not the most parsimonious of health maintenance organizations with respect to specialists. Some regions of the country are even more heavily endowed with specialists than the national average. In New York State, for example, there are 190 specialists for every 100,000 residents. Given the rapid pace with which managed care is expanding, fewer and fewer specialists will be able to maintain busy practices.

Universal access to health care would ameliorate this problem. Unlike the present system, underserved populations would have access to high-quality primary care and to appropriate referral for specialty evaluation and treatment. Thus, more people with symptomatic coronary artery disease would be referred for diagnostic angiography and, when indicated, for surgical intervention. Specialists would be able to provide their services to all who could benefit. Although it would almost certainly not eliminate the problem of surplus specialty physicians, universal access to care would surely reduce its magnitude. Do we really want to waste the investment we have made as a society in the production of so many well-trained specialty physicians when we know that many more of our citizens could have their health improved by the judicious application of their knowledge and skills?

Affordability

It is clear that providing universal access to the full range of effective health care services will increase health care costs for those who are now underserved. This fact brings us squarely to the problem of the affordability of universal access to health care. Is it possible to control cost and expand access at the same time, without compromising quality of care?

Let us first dispense with the myth that providing increased primary and preventive care services will reduce health care costs for underserved populations. This is an attractive proposition, often espoused uncritically by advocates for universal access to care and not infrequently accepted by politicians. It is unequivocally fallacious. Only two health care services result in reduced cost when provided widely: immunizations and prenatal care. All other health services, including other preventive services, increase cost (4). They may improve health, but they invariably do so at increased expense. This is true whether one assesses preventive services such as mammography, colon cancer screening, or cholesterol screening or therapeutic interventions that have been proved effective in improving outcomes like the treatment of hypertension, coronary bypass surgery for angina patients with left-main coronary obstructive lesions, or adjuvant chemotherapy for early-stage breast cancer.

Although appealing on the surface, careful analysis shows why the argument fails. It may be true that for a particular individual with hypertension, whose treatment prevents a stroke and its associated expensive treatment, total health care costs can be reduced by controlling blood pressure. For the entire population of individuals with hypertension, however, two crucial factors intervene to prevent this occurrence from being generalized. First, one must spend considerable resources in today's dollars to treat large numbers of people. Second, "savings" (in the form of prevented strokes and other expensive complications) occur only for a small fraction of the whole group and appear many years in the future, when dollars will be worth less, because of inflation, than they are today. Thus, when all the accounting is done (and the "savings" are discounted in present-value calculations), the net effect is, as the cost-effectiveness research studies consistently conclude, that effective health services cost money.

Not only is it erroneous to argue to the contrary, but I believe that it is also politically dangerous. Although it may be possible to persuade some politicians in the short run to support health care programs with the argument that they will save money in the future, this is a risky strategy. Such support will prove evanescent and will disappear predictably when circumstances dictate budgetary constriction and advocates are unable to document real savings. Advocates for universal access are better advised to make their case on the strength of the good that will come from the improved health of underserved individuals and communities.

A Quality Solution

I believe that there is a strategy that would permit us to provide universal access to health care without increasing spending or impairing quality. It is a strategy that focuses on quality of care and looks for solutions to specific quality problems as ways to control costs. There are three varieties of quality problems: overuse, underuse, and misuse (5). Overuse refers to the provision of a health service when its risks exceed its benefits. Underuse is the failure to provide a health service in circumstances when it would have provided a net benefit. Misuse occurs when an effective health service was selected but was then performed poorly so the patient failed to receive its full potential benefit.

Examining quality of care this way helps explain its relationship to health care costs. Improving quality can increase or decrease costs depending on what kinds of quality problems are addressed. Solving overuse problems reduces cost, but solving underuse problems increases cost. Although the data are less than ideal, evidence is accumulating that documents the cost-reducing impact of solving misuse problems. This is analogous to the industrial quality management dictum of "doing it right the first time."

The research literature documenting overuse is extensive. From the simplest interventions (e.g., ankle radiographs or oral antibiotics) to the most complex (e.g., upper gastrointestinal endoscopy or carotid endarterectomy), overuse abounds in American medicine. I believe that a conservative reading of that literature leads to the conclusion that we could eliminate about 20% of what we do in health care and quality would improve, because patients would be spared the unnecessary exposure to the risks of inappropriate interventions.

In addition, the evidence suggests that misuse problems are also important causes of poor quality care. The Harvard Medical Practice Study estimated that 4% of hospital admissions in New York State in 1984 were associated with an adverse event, which was defined as an injury caused by medical treatment (6). More recently, two of the most prestigious hospitals in Boston reported a rate of adverse drug events, defined as injuries resulting from medical intervention related to a drug, of 6.5 per 100 admissions, or nearly 2000 injuries per hospital annually (7). A growing number of studies demonstrate that improving care by ameliorating misuse can reduce costs significantly while improving quality. For example, avoiding postoperative wound infection by optimal use of prophylactic antibiotics leads to reduced cost because of fewer serious infections that need to be treated and because of shorter lengths of hospital stay.

Systematically addressing overuse and misuse problems would generate sufficient savings so that we could fund universal access to necessary and appropriate health care without increasing health care expenditures. A host of practical problems must be solved to implement such a quality improvement strategy effectively, but there is every reason to believe that the potential savings are sufficient to reach the goal of universal access without increasing costs.

References

1. Anderson GM, Grumbach K, Luft HS, et al. Use of coronary artery bypass surgery in the United States and Canada. Influence of age and income. JAMA 1993; 269: 1661–1666.
2. Schroeder SA. The latest forecast. Managed care collides with physician supply. JAMA 1994; 272:239–240.
3. Weiner JP. Forecasting the effects of health reform on US physician workforce requirement. Evidence from HMO staffing patterns. JAMA 1994; 272:222–230.
4. Russell LB. The role of prevention in health reform. N Engl J Med 1993; 329:352–354.
5. Chassin MR. Quality of care: Time to act. JAMA 1991; 266(24):3472–3473.
6. Brennan TA, Leape LL, Laird N, et al. Incidence of adverse events and negligence in hospitalized patients: results from the Harvard Medical Practice Study I. N Engl J Med 1991; 324:370–376.
7. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. JAMA 1995; 274(1):29–34.

Public Policy

A Doctor's Perspective

Kurt Hirschhorn, M.D.

I AM CERTAIN that it is clear to all of you that within your own professions you cannot find a single view that is held unanimously by all members of the profession. The same is true for physicians. Therefore, what I will present to you should be viewed as my perspective, which is shared by some but certainly not all physicians.

To examine access to health care, one must divide the term access into absolute and relative access. By absolute access I mean universal availability of health care of similar high quality to the entire population. Similar quality is, of course, the issue in all aspects of access, and I will return to this topic when discussing the various forms of relative access. Clearly, absolute access would require universal insurance of some form, either national, regional, or state. In theory it may be possible to have private for-profit insurers participate in universal insurance, but in my view there are problems with this approach. Confidentiality of perceived risk factors would be breached, potentially resulting in "cherry picking," leaving the sickest patients to some governmental safety net. The added expense to the government, along with the profit motive of private insurers, would keep health care costs very high.

Currently, such insurers and health maintenance organizations (HMOs) put 25 to 30% of receipts into their shareholders' pockets at the expense of the patients or their employers. The leaders of these organizations are paid unconscionably high salaries, often millions of dollars. By eliminating this profit factor, universal insurance of one form or another could immediately significantly decrease the cost of health care. Because cost factors have become a major driving force, if not the principal goal in reorganizing health care, it is essential that the inefficient and bloated bureaucracies of many governmental programs be addressed in preparation for such a huge undertaking. I realize that universal access is not something that will happen in the immediate future, but for a variety of reasons it must happen in the United States within the next 5 to 10 years, as it has in the rest of the developed world.

Relative access has many difficulties. There are various types of relative access. The most unacceptable feature of these arrangements is that many people have no physician of record. This system has increased health care costs and dissatisfaction. Costs are increased because uninsured and underinsured people seek their health care in emergency rooms, often when they are already quite ill. When primary care is given in emergency rooms, it is very expensive and does not lead to health maintenance. People are dissatisfied with the care because the caregivers in the emergency room do not know them, the experience is time consuming, the surroundings are usually unpleasant, and there is generally little follow-up. This often leads people to visit a variety of emergency rooms, increasing the lack of continuity, and accelerating the cycle of illness which may have been preventable by proper continuity of care. The end result is hospitalization, usually in a hospital of last resort or in other hospitals which must find financing for these unfortunate uninsured or underinsured patients.

Another difficulty with this system is quality of care. The measurement of quality depends on who does the measuring. Should it be measured by patient satisfaction, by some form of outcome criteria, or by a combination of the two? Clearly,

---

Address correspondence to Kurt Hirschhorn, M.D., Professor of Pediatrics and Human Genetics, Mount Sinai School of Medicine, New York, NY 10029.

quantitation of quality is complicated. Certainly a major criterion should be effective and timely availability of specialized services when they are necessary or advisable. With appropriate criteria, such services must include the life-saving, high-technology procedures which have been developed and proven effective by research. These include bone marrow and organ transplants; highly specific drugs; and, in the next few years, even gene therapy, if effective and necessary. Gene therapy certainly has the potential for being cost effective in the long run if it could essentially cure such chronic diseases as cancer, acquired immunodeficiency syndrome, and inherited problems. Another aspect of quality would require the evaluation of physician performance, both by patient response and objective criteria, with reeducation when performance is not satisfactory. Certainly recertification both in general medicine and in the specialties is fundamental to maintaining quality of care.

An example of the breakdown of proper care caused by the rules superimposed in the present system of HMOs is discussed in a recent article by Weston and Lauria in the *New England Journal of Medicine* (1). A 3-month-old girl from a working family received a diagnosis of a particularly severe form of leukemia, which was potentially curable by a bone marrow transplant. She was fortunate because her sister was a good match, but the HMO selected a "center of quality" in another state and would not support the transplantation in either of two nearby experienced institutions. Over the long run, the HMO's enforcement of this decision resulted in both parents losing their jobs; psychological difficulties with both children; and, as a final blow, loss of continuity of care when a second transplant became necessary and the HMO had changed to yet another "center of quality."

Equity and quality of access also become problems when people are told to change from the physician of their choice and are assigned a new physician or relegated to a clinic. This problem could be solved by having all physicians on salary, based on years of experience, specialty, geography, patient load, etc., so that the variation in cost would be abolished. By eliminating the current vast income differences among various groups of physicians, sometimes as much as 10- or 20-fold, all people would have the opportunity for equal access independent of availability and geography and they would have the benefit of establishing a doctor-patient relationship. Such a system would also greatly curtail current attempts to seriously delay or refuse referrals to appropriate specialists, purely based on cost.

Another recent paper in the *New England Journal of Medicine* by Levinsky (2) makes the point that the current social, institutional, and economic barriers to universal and high-quality health care violate patients' rights to informed consent. Informed consent has become a guiding principle of the doctor-patient relationship and has ameliorated the perception of the physician as authoritarian and motivated by economic self-interest. The growing power of insurance companies and managed care organizations has interfered with informed consent. Prohibiting the physician from informing the patient as to the economic rules of a particular HMO violates the principal that patients must be fully informed. These points were also stressed in a paper by Emanuel and Dubler (3) and by the Report of the Council on Ethical and Judicial Affairs of the American Medical Association (4).

Another problem of access involves differentiation between access to basic health care and access to extended health care. In a recent article in the *New York Sunday Times* magazine section, there was a story regarding the enormous fiscal problems of the outpatient department at Bellevue Hospital. One of the suggestions for saving money was to reduce the drugs available in their formulary to a basic minimum. It was suggested that Accutane, a drug used for severe scarring acne, could be taken off the formulary. Does that mean that it is all right for poor people to have scarred faces whereas those who can afford a private physician can look beautiful? Hidden in this question is the risk that these poorer patients could then be discriminated against additionally when seeking a job in which appearance, at least in our society, becomes an important factor. Many people agree that some limits must be put on what is available in health care; I will return to this problem later.

Access or degree of access is relative when it comes to HMOs. Both nonprofit and for-profit HMOs limit the use of specialists, but for-profit HMOs cause a special problem because they use inducements. There is something fundamentally wrong in making good primary physicians' incomes dependent on their referral pattern, independent of medical criteria and clinical judgment. Furthermore, making primary care physicians into gatekeeper physicians is a counterproductive policy. HMOs do not recognize that early involvement of a specialist in many cases is better for health and for costs than calling upon the specialist only when the patient crashes. Long experience in developing what is considered the foremost medical care in the world has taught us that the increasing complexity of our knowledge requires early and continuous interaction between the primary physician and the appropriate specialist. For example, early referral of an at-risk individual to a cardiologist for evaluation of cardiac function by a variety of stress tests clearly leads to the application of preventive measures designed to decrease the risk of a heart attack.

In my own field of medical genetics, it has quickly become clear that primary physicians cannot possibly keep up with the exponentially growing knowledge of genetic conditions. In addition, their busy practices do not allow them to spend the great amount of time needed to obtain a complete family history or to spend the many hours required for appropriate counseling of patients and their families. Important patient decisions about obtaining information on family members, about whether or not to test for detrimental genetic mutations, and about reproduction turn on providing patients with sufficient understanding to allow them to consider the appropriate issues. It is only by early referral to the appropriate specialist that future tragedies, costly both in money and suffering, can be avoided. When such referrals lead to decreased income for the primary physician, the policy in many for-profit HMOs, the patient will suffer. Matters are made even worse when the physician is not even permitted to inform the patient that the physician's referral and treatment decisions have an impact on their own reimbursement.

What is the solution? Appropriate access to health care requires universal insurance, whether governmental, private not-for-profit, or a combination of these, free choice of primary physician, salaried physicians, careful monitoring of quality of care with retraining of physicians when necessary and recertification as a rule, and eventually some form of limits. Any limitation on treatment and referral must be based on research to establish criteria. A few examples of appropriate research questions are when to perform a computed tomographic scan or magnetic resonance imaging for head injury, or where and with what fluids to rehydrate infants and children with diarrhea and vomiting. A current, particularly severe problem is geographic variation in care. Recently, for example, it was shown that lumpectomy or mastectomy for breast cancer and back surgery or physical therapy for back pain vary enormously from region to region in the United States. Again, research results must be the guide for practitioners in these and many other treatments.

I hope that in the not-too-distant future we can approach these humane goals. With physicians, patients, and the government participating, we should be able to achieve universal access to high-quality health care. The result would be an improvement of the health of the population at more reasonable costs to the country.

References

1. Weston B, Lauria M. Patient advocacy in the 1990s. N Engl J Med 1996; 334:543–546.
2. Levinsky NG. Social, institutional, and economic barriers to the exercise of patients' rights. N Engl J Med 1996; 334:532–534.
3. Emanuel EJ, Dubler NN. Preserving the physician-patient relationship in the era of managed care. JAMA 1995; 273:323–328.
4. Council on Ethical and Judicial Affairs, American Medical Association: Ethical issues in Managed Care. JAMA 1995; 273:330–335.

Panel Discussion

Issues in Medical Ethics

Rosamond Rhodes, Ph.D., Afternoon Moderator

Prof. Rhodes: Now that we have heard from all of our presenters, we have an opportunity for the panelists to interact with one another and with the audience. We must try to put the religious and philosophical insights together and see how they fit with recent American attempts at health care reform. We must try to understand how the various theoretical positions apply to the decisions that have to be made.

Prof. Buchanan: I have a minor question for Dr. Hirschhorn. I'm happy to hear a well-established physician making such progressive proposals. Ten years ago we would not have heard this from most physicians, especially the suggestion of having physicians on salary. We still don't hear this from most physicians and, although I think it's probably a good idea, there is a standard objection to it; each form of compensation has its own virtues and vices. The obvious objection to salary compensation is the risk of people shirking, which is just one kind of agency risk.

Dr. Hirschhorn: I have heard that many times. I have lived all my life as a salaried physician in an academic environment and few have accused me of shirking. My colleagues in the health center work very hard in a combination of activities including seeing a large number of patients. I think that the risk of shirking when salaried may be true for certain people who are going to gold brick no matter what, and that is just unfortunate and has to be watched. That is why I stressed that monitoring, quality of care, and quality of performing care has to be evaluated and reevaluated. One of the aspects of salary certainly has to be patient load. If all you are going to do is see one patient a day, then you should not be getting the same salary as the individual who has a full clinical load. The main advantage of having physicians on salary is that it would allow us to do away with the vast differences in income among physicians. This, more than the excess of specialists, which I agree is a problem, has been a major reason for the enforced reduction of referrals in HMOs. Such referrals cost a great deal because of the current established reimbursement of specialists. I think such differentials should be abolished.

Prof. Buchanan: From the studies and anecdotal information I have seen there is not quite as much difference as you suggest between the behavior of not-for-profit HMOs and for-profit HMOs. A priori, you might think there would be a big difference. In fact I think in terms of the reimbursement arrangements that place physicians in conflict with the interests of their patients, that distinction is beginning to blur and for quite some time there have been data suggesting many so-called not-for-profit health care organizations behave, look, smell, act just exactly like for-profit organizations.

Dr. Hirschhorn: I agree, but there is one vast difference and that is that 25–30% of the profits go into the pockets of shareholders. Another definite difference, which still exists, is in the salaries paid to the leaders of the two types of organizations. Although the salaries of CEOs of not-for-profit HMOs are not exactly small, they do not reach the five to fifteen million dollar range that you find in the for-profit organizations.

Prof. Buchanan: The record is one hundred and thirty-seven million.

Dr. Barbasch (audience): In speaking of the access to specialist care I would argue that the reason specialists act as primary care givers is not because of the reimbursement difference but rather the costs incurred when they order more sophisticated and expensive tests. Specialists are eager to confirm their diagnosis as soon as possible.

Dr. Hirschhorn: It sounds as though there has been a misunderstanding. I did not say that specialists should be primary care physicians, I said

---

Associate Professor of Medical Education, Director of Bioethics Education, Mount Sinai School of Medicine.

that the interaction between the primary care physician and the specialist should be easy, early, and appropriate. I would in no way agree with the view, as expressed for many years, that it is necessary for the cardiologist to be a general internist. Therefore, we would need fewer cardiologists than we have now, because most of them in fact do not act as cardiologists, they act as general internists and they make believe that they are primary care physicians. What I meant is that the services and expertise of the specialist should be easily available to primary care physicians whenever they have a specific question in mind. Access to specialists should be easy. You can't just ask for a consult, you've got to have a specific question. I teach this principle to my residents when they ask for a consult in pediatrics. What we have to do is to teach all physicians, not only the primary care physicians, how to phrase specific questions in order to utilize specialists appropriately.

Dr. Barbasch: We have no argument about that. Very often the ones who are accused of overutilization are those treating chronic diseases, such as AIDS, cancer in which a lot of research goes on. It takes time to gather the data on a large scale and there are thousands of abstracts that are published every year about the latest, newest, and the best for any of these conditions. When dealing with terrible illnesses in which, very often, there isn't much time, how do you prevent overutilization when there are these reports that come out that really force us to switch over from standard treatment.

Dr. Chassin: That question points out the two different kinds of overuse. There is overuse in commonly done, long-standing treatments or interventions, like tonsillectomy or x-rays for injured ankles, where there is not a whole lot of new information pouring out every day. There may not even be a lot of old information about what works and what doesn't. In fact that is a significant problem in trying to deal with any of these judgments about what ought to be covered and what ought not to be covered. There are several interesting studies which suggest that only about 10–15% of what we do in health care has been proven, by scientifically rigorous data, to be effective. This doesn't mean the rest of what is done is harmful or wrong, but it means using it rests on something other than really good scientific data. So one kind of overuse of commonly done procedures could be addressed with guidelines and ways of summarizing what we clearly know does and doesn't work and what, in fact, does harm. If you define overuse that way, the literature shows overuse, on a conservative reading, of about 20%. That does not include the areas in which physicians disagree, in which there are not any good data, in which reasonable people can take different positions and we really don't know what the final word is.

The area that you have addressed specifically, new information and interventions, is the single most important factor in the rate of increased health care costs. There are two health care cost problems. One is the amount of money we spend today, 14–15% of gross national product (GNP); a lot of money, about one trillion dollars; but the more important problem is how fast that level of expenditure is rising. Health care costs have been rising faster than costs in every other sector in the economy for 50 years. This is not a recent phenomenon. Even though the rise in cost has slowed, so has the rate of inflation and so the multiplier is still there. There is still a faster rise in costs in health care than in the rest of the economy. The chief reason is all the new items and procedures that we put into the system every year. Health care today is a very different package of goods and services than it was 5 or 10 years ago and in large part what you've questioned is representative of that phenomenon. We are very inventive and creative. No one does it better than we do but we are awful at evaluating these inventions and creations and at figuring out when they really work to provide better outcomes for people than the next best thing or the older treatment. We are even worse at limiting their use to those areas in which they have been proven to be effective. I would argue that we need a much more systematic approach to the evaluation of new ideas. Many new ideas, even though they look promising at first report, turn out to be completely ineffective, or even harmful. If you leap at the first report of something that looks effective and use it immediately, in the long run you are much more likely to be doing harm than if you waited and were a little more judicious. We need a much more systematic attempt to evaluate our new ideas, and then we need a way of communicating, not by rigid prescriptions or regulations, but in a much more user-friendly, practice-based approach. The use of new interventions should be limited until they have been proven effective.

Dr. Rhodes: Let's shift gears and get back to the response of organized religion to the question of access to health care. Part of my motivation in designing this conference had to do with concerns about the religious right. We have seen the rise of the religious right, and everybody seems to be talking about them. They identify themselves as religious, they tend to be extremely right wing, and, unlike the panel, they are not advocates for universal health care. Is there something coming out of your religious tradition or out of our society that you think accounts for this kind of movement and the failure of religion to inculcate the positions you've explained?

Rev. Forbes: I have known members on the right and members on the left. For a while I sensed that liberals tended to be of a higher economic class than the members of the right. There was a strange capacity for the liberals to harbor a sense of contempt for the person who happened to be in a different class. Therefore, there was not the response to questions, anxieties, fears, and the stigmatization of their class. Then when they found somebody who listened, albeit politically right wing conservatives, they formed a new alliance. People are likely to affirm the views of those who share their concerns. First, there was a polarization along class lines that has something to do with sympathy. Second, within organized religion there is often a higher incidence of faith that is expressed in terms of accepting multiple ways for addressing health care. If you have a Pat Robinson on television and he is praying for you, it is almost to his advantage to have people more interested in a faith healing rather than in the broader process of healing.

Dr. Rhodes: So, does a church in every community count as health care?

Rev. Forbes: What we find to be of interest to ourselves influences the content of our ideology. Ideology makes for strange bedfellows. The issues often raised by the conservative right are issues to which those of us who are progressive will have to learn to respond. We will also need to learn to reach out to those classes of people who are not populating our places of worship.

Rabbi Wechsler: I might add that I think one of the differences has to do with the extent to which we, as individuals, assume that the government is the obvious solution to the problems we have noted. Some of us have come out for universal access to health care but without saying that the government is the way to go. I want to make a strong statement that there ought be universal access, but I'm not really quite sure how to go about implementing it. I'm glad to see that there are others of you thinking about it who know a lot more about the facts than I do. The job of the moral theologian is not to solve the problems in the market place. Our job is to state what our aspirations as a society ought to be. We should speak about the goals rather than how we ought to achieve those goals.

The religious person really has a contract with God. It is that contract between the individual and God that has got to be worked on and observed. That's the challenge of life.

As for the religious right, my perception of their position is the less government the better off you are. I think there is suspicion of government. That's been my reading about why the religious right has kept away from governmental solutions. At the same time, I want to say that because I have come out clearly for universal access, I do not equate that with the assumption that there is only one way to achieve it.

Monsignor Fahey: I can speak about nothing other than the Roman Catholic tradition. We're so mixed up in many ways. The Church hierarchy in the United States is progressive socially but conservative theologically. There is a determined effort on the part of the religious right to capture a number of Roman Catholics within it, although it has been quite unsuccessful. However, they have built what they call a Catholic Alliance. Virtually everyone in the hierarchy, even the theologically conservative, find their use of that name objectionable. Within our tradition, a grass roots group that's relatively small, Catholics United for the Faith, takes exactly the opposite position.

The Catholic Church historically has been the Church of poor working people. Gradually it has become more affluent. The sons and daughters of the last generation went to Fordham and Saint Johns. Now their sons and daughters are going to Harvard and Columbia. The Church congregants are now a more socially and economically mixed group. The religious right we are hearing from is mostly a Protestant phenomenon. Ironically, to a large extent, a lot of its membership are affluent.

Prof. Rhodes: So you don't agree with Rev. Forbes.

Monsignor Fahey: No I don't really. I think it's an affluent group with a protect-ourselves sort of mentality and a libertarian philosophy. Some of the things they are saying about the ability of the Church to pick up the social services function makes me think they are out of their minds. Having been involved with Catholic Charities for 35 years and with parishes for 35 years, I know the idea that churches and synagogues have the ability to fulfill basic welfare functions is just absurd.

Rev. Forbes: Among the religious right, there may well be significant numbers of affluent among them now. The movement's historical trajectory suggests a much poorer social background. Although they have developed a higher economic range, they still reflect their former condition of servitude. I do not think that they are the old guard. Perhaps they are from the nouveau riche, looking at the benefits of both regional and ideological identifications for the continuation of their economic ascendancy. I think that's a factor as well.

Dr. Hirschhorn: Isn't it true that if you were to say the extreme right derives from the poorer classes that you might expect a rather large number of minorities among them, when in fact quite the opposite is the case. They are anti-black and Hispanic and so on. It doesn't seem to quite fit.

Rev. Forbes: When you are from down South you begin to recognize that the race factor always skews any kind of normal expectation.

Issues in Medical Ethics: 1997

Reproductive Choice:

Genetic Counseling and Assisted Reproductive Technology

TWELFTH NEW YORK REGIONAL CONFERENCE
MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK
FRIDAY, MARCH 7, 1997

Moderators

Rosamond Rhodes, Ph.D.
Associate Professor of Medical Education
Director of Bioethics Education
Mount Sinai School of Medicine

Daniel A. Moros, M.D.
Associate Professor of Neurology
Mount Sinai School of Medicine

A History of Eugenics and Genetics
Kathy J. Cooke, Ph.D.
History Department
Quinnipiac College

A History of Assisted Reproduction and Abortion
David A. Valone, Ph.D.
History Department
Quinnipiac College

Genetic Counseling and Today's Patient Options
Judith Willner, M.D.
Associate Professor of Human Genetics and Pediatrics
Mount Sinai School of Medicine

Assisted Reproduction and Today's Patient Options
Maria Bustillo, M.D.
Associate Clinical Professor of Obstetrics, Gynecology and Reproductive Science
Mount Sinai School of Medicine

Prediction Certainty and Statistics: Genetic Screening and Reproductive Technology
Kelly C. Smith, Ph.D., M.S.
Assistant Professor of Philosophy
College of New Jersey

Multifetal Pregnancy: Difficult Choices for Patients and Their Doctors
Richard L. Berkowitz, M.D., M.Ph.
Professor and Chairman of Obstetrics, Gynecology and Reproductive Science
Mount Sinai School of Medicine

Reproductive Choice and Public Policy: A Doctor's Perspective
Kurt Hirschhorn, M.D.
Professor of Pediatrics and Human Genetics
Mount Sinai School of Medicine

A Philosophic Perspective on Reproductive Choice
Patricia Mann, Ph.D.
Assistant Professor of Philosophy
Hofstra University

A Sociological Perspective on Reproductive Choice
Barbara Katz Rothman, Ph.D.
Professor of Sociology
The Graduate School and Baruch College, City University of New York

Cases and Doubts
Randi Zinberg, M.S., M.S.
Human Genetics
Mount Sinai Medical Center

Barbra Bluestone, M.D.
Department of Medicine
Mount Sinai School of Medicine

Panel Discussion

Can Age-Based Rationing of Health Care Be Morally Justified?

MICHAEL M. RIVLIN, M.A.

RATIONING OF HEALTH CARE is inevitable. Callahan (1) and Daniels (2) have both made suggestions about rationing by age, but only under circumstances that cannot be achieved for many years, if at all. The medical profession, however, must make choices concerning patients now. At first sight, using age as a justification for rationing is appealing because it is objective and easy to establish. Moreover, many of the methods currently being used for deciding the distribution of funds depend on value judgments which are vague and disputable (for example, "quality of life"). Appeals to justice, fairness, and intuition seem to support the idea that finite resources should be directed at the young, who have not had a chance to live their lives, in preference to the elderly who have already lived a major part of theirs. Arguments for aged-based rationing (ABR) either can be based on determination by reference to data or grounded in philosophy. In this paper three of the most frequently used philosophical justifications for ABR, i.e., the "fair innings argument," the "natural order argument," and "potential years," are examined and found to be inadequate.

In attacking ABR I am not kicking at an open door. In the United Kingdom ABR is practiced both overtly and covertly. Dr. Shaw (3), a consulting physician writes, "Ageist policies are in current use and open discussion of them is advocated." Later in the same article he states, "Ageism flourishes in British hospitals." In addition to such explicit rationing there is also an insidious movement toward making ABR acceptable that is almost imperceptible and very worrisome. This movement usually starts out as a denial that ABR is acceptable; therefore, refusing treatment because of a patient's age should be deplored. But it is not long before the "sting in the tail" appears. The argument usually takes the following form. "ABR is not something to be tolerated. Discrimination by age, like that of sex and race should be rejected. However, if a choice has to be made between two patients, and the only difference between them is their age, then although we are against ABR, it is permissible (if there are no better alternatives available) to give the treatment to the younger patient."

Let me a give an actual example of where this insidious ABR occurred recently. Roger Crisp, a philosopher and respected writer in medical ethics, presented and endorsed (together with David Ebbs and Tony Hope) in the *British Medical Journal* a draft policy document prepared to assist a practice of general practitioners in clarifying the ethical basis for the rationing decisions it inevitably has to make. The policy document emerged as a result of lengthy meetings between the partners of the practice and Crisp and his colleagues. Regarding ABR, Crisp and his colleagues write, "We do not wish to deny treatment on the basis of age—that is the partnership rejects any policy that states that no one over a particular age should ipso facto not be allowed a specific treatment. Hospitals, however, which are not controlled by the partnership, may operate a policy for some treatments. But the partnership will do what it can to ensure treatment and will not itself deny treatment on the basis of age." (4) If Crisp and his colleagues had finished their com-

---

Part of this material was presented at a conference on "Is Age-Based Rationing a Moral Option?" in Leeds, England, 25 June 1996.

Address correspondence to Michael M. Rivlin, M.A., Ph.D. Candidate, Department of Philosophy, University of Leeds, LS2 9JT England.

ments on ABR here I would have absolutely no criticism of the position they took. It is hard to see how they could be more emphatic about not wanting ABR to be a part of any rationing policy of the practice. Unfortunately, there soon comes the "however" referred to earlier which shows that their claim that ABR should not be permitted is little more than a fig leaf that covers their real views on the subject (4).

Crisp et al. continue, "Situations may occur rarely in which the partnership has to choose which of two patients should have priority in receiving some beneficial and expensive treatment. In such cases a decision about how to proceed will be made at the partnership meeting. It will be legitimate to consider any factor that can be considered at least potentially relevant to making a decision. This does not imply that any factor that can be considered will be thought relevant in a specific case. For example the patients' ages may be considered and found relevant. This is because the partnership believes that two ethical values may be relevant: (a) how long each patient is likely to live to enjoy the benefit of the treatment (a value endorsed by the QALY [quality adjusted life year] perspective), and (b) 'the fair innings argument,' which the partners consider to have some weight. The fair innings argument suggests that to treat the older person, letting the younger person die, would be inherently inequitable in terms of life lived: the younger person would get no more years than the relatively few he had already had, whereas the older person . . . will get several years more." It will be seen clearly that this is a case where it is first stated that ABR should not be countenanced as a method of rationing, but before very long this view is qualified (no pun intended) by the suggestion that age is a relevant consideration that may legitimately be considered in the allocation of health care. It is by such methods that ABR becomes acceptable (4).

The Fair Innings Argument

There are good reasons for emphasizing the importance of fairness in any discussion of rationing. (Throughout this paper I will be using "fair" to refer to whatever is not "unfair." As John Stuart Mill wrote, "for justice like many other moral attributes is best defined by its opposite" [5]). Even in the United Kingdom, where there is a National Health Service, patients have a very limited legal right to treatment, and the question of what moral rights there are to treatment is even more problematic, but it is surely less contentious to suggest that treatment should be distributed fairly. Many of the philosophical arguments used to justify ABR are based on the notion of fairness. The fair innings argument, for instance, the strongest weapon in the ageist's armory, depends on a particular understanding of what fairness is for its strength. Although it would be helpful to define accurately what makes something fair before engaging in our discussions, better people than I have attempted to find a definition and have failed (6). However, it seems clear and uncontroversial that we can base a discussion about the merits of age-based rationing on the fact that it would be unfair to deny equal access to treatment unless there is good cause to do so.

The fair innings argument is based on the suggestion that it would be unfair to deny the young the opportunity to become old while allowing those who are already old to become even older. There are actually two arguments involved: the first states that we should always prefer the younger of two patients; the second states that we should deny treatment to an elderly person only after he has achieved a full life. I will discuss both of these in more detail. However, I am not convinced that when we say that young people should be given the opportunity of reaching an old age (at the expense of giving further treatment to the elderly), we necessarily believe this to be the case. What may actually be underlying the thought is that it is right that some people should have the opportunity to reach old age, but not everyone. It is my contention that we think that there are people who should be given the chance of achieving a fair innings, but we may also feel that others should not. There are situations in which our views about whether the young should be treated in preference to the old will depend on the value we place on the individuals concerned. If we were to examine our feelings more closely in these matters it would be realized that what is actually at issue is our thoughts about the individual concerned, not that everyone should be given an opportunity to achieve a fair innings.

Underpinning the fair innings argument is the idea that it would be tragic if a young person died, but only unfortunate if an elderly person did. Although we can understand the intuitive appeal of this assertion, the argument breaks down when we examine the feelings we have toward the death of a 25-year-old drug pusher versus the death of the 70-year-old grandparent who is doted on by his children and grandchildren. (Any one who heard Rabin's granddaughter's eulogy at his funeral would realize the importance that there can be to such a relationship.) Would we be so ready to think of the young criminal's death as being more of a tragedy than that of the grandparent?* I suspect that we would not; and, if this is the case, then the fair innings argument collapses into a social argument about our perception of a person's worth and value, based on our appraisal of his lifestyle. The fact that he is young does not, after all, seem to be the most important factor to be considered when allocating health care.

There are other examples that illustrate this point. Consider the situation in which two people have been killed in an automobile accident, one a joy rider who had stolen a car, and the other a doctor or nurse into whom the joy rider had crashed. Would we feel it was more of a tragedy that the driver of the car was killed even if we were told that he was the younger of the victims? I doubt if we would. Therefore it seems that it is not only the long innings argument that is the consideration, but our views of the people concerned.

It may be suggested that the few cases I have referred to are so unusual that one should not decide policy based on them. (Hard cases make bad law.) But I would disagree with this criticism. Recently the press in my home town reported the case of an elderly man who was pulled from his car, mugged, and dragged along the road by a young man, who then drove off in the victim's car. I do not accept that there are only a few such cases (although they may not all be as outrageous). On the same day it was widely reported in the media that two youths attacked and severely injured an elderly man because he remonstrated with them for breaking into a car. The newspapers (and prisons) contain many examples of young (or middle-aged) people behaving in a manner that would put in question the belief that everyone should have the chance of achieving a fair innings. It is worth noting here that in 1993 34% of men in England younger than 40 years of age had a criminal conviction (7).

I realize that what I am saying is contentious, but the fact is that, however much we may pretend otherwise, whether we believe someone should be given an opportunity to achieve a fair innings may well depend on our view of their "value" as a person, and not just on their age. We might like to think that doctors ignore social factors when treating patients but they do not. Evidence of this can be found in an article by Heller et al. (8). In a survey conducted of 4924 patients on the variations of resuscitation attempts after cardiac arrests they report that "resuscitation was more likely to be attempted in younger people and those with a higher level of education." This article illustrates that whether or not treatment is given is often decided on criteria which are not strictly medical. It must be emphasized that I am not advocating that we should award or deny treatment based on our views of a person's worth—the consequences of doing so are morally abhorrent, and far too dangerous. But it seems to me equally abhorrent to deny treatment to elderly patients for no other reason than they had achieved a particular age.

Before we lightly dismiss the idea that we do give importance to our views of the worth of an individual, Judith Jarvis Thomson shows how our perception on a seemingly straightforward situation changes when all the facts are known. Commenting on Philippa Foot's famous "trolley problem" (9), in which a trolley is hurtling down a railway track toward a group of five workers but can be diverted by a passer-by on to a track where there is only one person, Thomson writes, "In short, an account of what makes it permissible for Bloggs [the passer-by] to turn the trolley . . . is going to have to be sensitive to differences in how the six came to be where they are on the tracks: it must yield that the trolley may be turned in the case of some histories and not others." (10) Intuitively we may think that the observer should turn the trolley, but would we feel the same if it were known that the five were escaped convicts, and the one the policeman chasing them? It is obvious how this example can be used in a medical context when having to choose between patients.

As noted, the fair innings is not one argument, but two. The first argues that the younger patient should always be preferred. (This is the view of, for instance, Kappel and Sandoe (11) who argue that we should always prefer the younger patient when it comes to the distribution of resources.) If this "hard version" of ABR is accepted it would of course mean giving preference to a 6-year-old instead of to a child of 6 years and 1 month. This would force us to agree that some decisions may arguably be very strange and contentious. Besides meaning that one person would be preferred to another just because he was a few weeks younger (Can this really be thought of as a sensible way to allocate a life-saving resource?), young people with a poor prognosis who require very expensive treatment would be preferred to those elderly who might require inexpensive treatment that would enhance their quality and quantity of life at little cost.

---

*I accept that the drug pusher's parents might regard the death of their son as a greater tragedy than that of the older person, but that is not the point. Age cannot be determined to be a more important criterion than other factors based on the parents' view of the death of their child.

Such cases pose great problems for those who advocate ABR. An example of this was highlighted by a recent case (Miss G) in England (12). Miss G is a 23-year-old woman who had been in a coma for more than a year. Her doctors, supported by her mother, were about to request permission from the courts to remove Miss G's feeding tubes on the basis that she was unlikely to recover, and that she had expressed the view shortly before her accident that should she ever be in such a situation, she would not want to be kept alive artificially. However, 3 days before the case was to be heard, two psychologists were able to communicate with her. Miss G, by pressing a button in answer to a question, signified to them that she wanted to be kept alive. It must be noted that 7 months later Miss G is still in the same state and, however much one sympathizes with her, it must surely be admitted that, by virtually any standards, her quality of life is very low.* This is a case with which those who advocate ABR must be prepared to deal. If the choice is between treating Miss G or a 70-year-old Mr. H who requires a coronary arterial bypass graft which would greatly enhance the quality of his life, why, it may be asked, should Miss G be given preference? Can it really be claimed that the only fact that should be considered when deciding which patient should be treated is "age" when other considerations are arguably so much more relevant? This case illustrates very well why factors other than age *should* be taken into account when deciding whether or not to treat a patient. The tragic situation of Miss G sums up much of what is wrong with ABR.

Of course, it might be claimed that, although it may be agreed that age should not be *the* consideration in the distribution of resources, it is legitimate to use it is *a* consideration. However, even this claim is open to dispute. Putting aside for the moment my contention that ABR is morally unacceptable, it would have to be shown what there is about age *per se* that it should be regarded as a justification for rationing. Surely it is not age itself that is important, but what being old might mean. It is here that misconceptions may surface: for instance, that age is synonymous with illness (it is not) or that elderly patients do not benefit from treatment (they often do and, in some situations, better than younger patients). Age could only be justified as a criterion if, as a result of being a certain age, treatment was not going to be effective. But if this were the case the justification for denying treatment has more to do with the notion of futility than of age.

The second argument suggests that everyone should be treated as equals with regard to health care until they reach the age considered to be a fair innings, and should only be denied treatment after they have reached that age. It assumes that people have an entitlement to a "normal life-span," and that diverting funds to the elderly might prevent younger people from attaining this span. To those who hold that view, in the example of the two children I referred to a moment ago, age would not be a consideration, it would only be so much later in life if one of them had achieved the age thought of as constituting a normal life-span, but the other had not. Up to that point age would not be an important factor because neither of them would have achieved their fair innings. But the suggestion that age should not be a consideration until a person had achieved a long life puts those who support ABR in a difficult position. Callahan writes, "Do the elderly have an unlimited medical claim on public resources? No, they have only a reasonable and thus limited claim. What is a "reasonable" claim? I take it to be a claim to live a long life with public support, but not indefinitely long, and not at the price of potential harm to others." (13) Note his use of "after a long and full life." But who is to decide when a person has achieved his ambitions, and may it not be that a younger person has had enough of life long before someone much older?

The assumption that it is always fair to treat the younger of two patients could also be challenged by considering the following example. There are two people competing for the same resource, one old and one young, and the younger person has already had a substantial amount of medical treatment, because, for instance, he is forever being involved in skiing accidents caused by his own recklessness, whereas the elderly person has looked after himself and not hitherto required any medical treatment. Where would the fairness be in denying the older person the treatment?

The Natural Order Argument

The natural order argument is based on the premise that old age and death are in the natural order of things* and therefore, like other things that are inevitable, they should be accepted and not resisted. Although there is an inevitability about growing older (there is of course no guarantee that we will grow old), we often are able to alleviate, or even cure, many of the illnesses that occur in the elderly. It must be emphasized that one of the principal aims of medicine is to fight against what is allegedly the natural order of things; not to do so might be thought of as incompatible with such aims. Callahan's views can be summarized as being that death at the end of a long and full life should not be thought of as an evil, but that it is simply the last stage of a person's life and is a natural and acceptable part of that life. Callahan writes (while discussing the concepts of a "natural life-span" and "a tolerable death"), "By these notions I mean a fitting span of life followed by a death that is relatively acceptable in its timeliness within that lifespan." (1) Because this is the case we should not unduly strive to lengthen life beyond a norm, but should instead try and ensure that everyone reaches, or at least is given the chance to reach, a normal life expectancy. A major problem here is how to decide what is a normal life expectancy. Life expectancy figures change frequently and the length of life a person can expect to live can depend on in which country, or even in which part of that country, they live.

---

*I am not suggesting that funds should not be made available to treat Miss G, only that it seems odd that she should be given preference over an older person who would benefit more from the treatment.

The feeling that there is some natural order which involves a human life-span, consisting of various stages culminating in old age and finally death, is expressed by the view that it would be a tragedy if a young person died but only a misfortune if an elderly person did. Callahan makes a similar point, ". . . while all death is a cause for sadness, a death in old age after a long and full life is, given the inevitability of death, the most acceptable kind of death. . . . It is no accident, I think, that there is less weeping at the death of a very old person than at the death of a child" (13). (Note that Callahan is not saying that we would want to weep less for a middle-aged, or even an old person, but only for a very old person.) The thought here is that it is worse for a younger person to die because theirs is a "premature death." There is some merit in this argument. It would be absurd to deny that if someone is enjoying life, the more of life they are prevented from having, the worse it is for them to be deprived of it. The crucial words here are "for them." On a personal level (and for their families and friends) it may be terrible that they will be unable to grow old. However, this does not make it right for us to deny an elderly person treatment because their remaining years may be very precious to them and to their families. At whatever age death occurs it may still be considered premature.

At first sight the natural order argument is very persuasive. Ageing (at the moment) is in the nature of things. It could be suggested that to deny the young resources to extend the lives of the elderly is so to speak "unnatural." I am not disputing that, as a parent, I would feel it more of a tragedy if one of my children died than if my remaining parent did, and presumably most people would feel this way about their families. (I am assuming here that there are no special circumstances such as family quarrels.) We age, we do not get younger. The obituary columns are filled with notices of deaths of the old as opposed to the young. The views of those who advocate ABR can be stated as "If to age is inevitable, then why try to fight it? Let us spend our finite resources on giving the lives of the elderly more quality instead of spending money on something "unnatural," i.e., trying to extend their lives beyond what is determined as the norm." But this ignores the fact that we are able to improve life in terms of both quality and quantity. The improvement is evident in the degree that life expectancy has increased during the past century. There may be a discovery just around the corner (an anti-ageing pill?) that will have a further dramatic effect on increasing life expectancy. Falstaff, in Henry IV Part 2, said, "We owe God a death." (14) But he did not say when that debt was due. "When" is being constantly postponed. One hundred years ago, "when" occurred much sooner than it does today. As we continue to improve both the quantity and quality of old people's lives, then what is considered to be the natural limit of a life will be further and further extended. In the past it might have been thought that when a person had reached the age of 50 they had achieved their natural life-span. Today it would be more likely for 100 to be considered a long innings, and who knows what it might be tomorrow?

If it is accepted that there may be a "natural order," it can legitimately be asked what relevance it has to the allocation of scarce health care resources. Those who propose ABR based on the natural order argument may suggest that if we do extend life expectancy beyond our wildest dreams (or fears) we would still have to take account of the natural order argument. It would be in the nature of things for the 150-year-old to die before the 130-year-old. But given that this is the case, it could still be argued that if elderly people were enjoying a good quality of life even at a very old age, the natural order argument loses much of its relevance.

---

*I wonder if we can be so certain that it is in the natural order of things for the old to die before the young. That certainly is not as inevitable as other events that are in the natural order, such as death, for instance.

Even if it will always be in the natural order of things for us to age, and for the elderly, as part of a "life cycle," to die before the young, increased life expectancy, together with improved quality of life, will mean that the way society sees the elderly (and how the elderly see themselves) might change dramatically. The term "old age" may then have no more pejorative baggage attached to it than would be attached to other age group. Some individuals believe that we should be content to accept what they believe to be the natural order of things, and that the elderly should come to terms with old age. The elderly should accept that old age is a part of life and that it should not be resisted. This is not the view expressed by Dylan Thomas when he wrote, "Do not go gentle into that good night, old age should burn and rage at the close of day; Rage rage against the dying of the light. Do not go gentle into that good night." (15)

Potential Life Years

It has a nice ring to it. We need look no further to justify ABR than to consider the lack of potential remaining years to justify denying the elderly patient treatment, that these potential years matter above all other considerations. However intuitively attractive this may seem, potential life years cannot really be seen as a good reason for applying ABR. It seems strange to give such a high priority to potential life years when other factors such as quality of life are taken into account. Why, for instance, should a young patient in a persistent vegetative state, or a patient in unremitting, or unrelenting, pain be given preference over an elderly patient with a better prognosis? Quality of life, although very difficult to measure, cannot, and should not, be ignored. It may be problematic to establish criteria for what constitutes a quality of life worth having for it to be used as a "tool" in deciding the allocation of treatment, but it seems odd to deny that quality of life should be thought of as being less important than potential life years. The case of Miss G, referred to earlier, may be thought to be an example of this. I would not deny that if the aim of medicine is to ensure as many people as possible have as many life years as possible, then there might be a case for giving overriding importance to potential life years, but this would depend on a view of the role of medicine in our society that few would hold.

We should not lightly dismiss the claim that it is worse for a young person to die than someone who is old. I would accept that there are situations in which potential life years do matter. No one would deny that a treatment that gave a person 15 years of extra life would be better than one which only gave 10 years of extra life. Assuming that these extra years are not to be spent in pain or crippling disability, the potential years gained are an obvious benefit. However, to admit this does not mean that we should decide which patient to treat on the basis of which one is likely to live longer, because, as we have discussed, other considerations may be of greater relevance. I suggest that although it might be worse for a younger person to die, that in itself is not a good enough reason to deny the elderly life-saving or life-enhancing treatment. One could also say, for instance, that it is worse for someone who is enjoying life to the full to die than for a person who is not, but it would be unthinkable to allocate treatment on such a basis. It must also be remembered that the question we are seeking to answer is not whether it is worse for a young person to die than for an older person, but whether or not we should award treatment based on the potential years someone may have to live.

Further, it might be suggested that if extra years were considered to be so important then the government should be encouraging people not to use contraceptives, and health care resources should be concentrated on giving *in vitro* fertilization treatment to everyone who needed it, because extra births would undoubtedly mean more potential life years. It would also follow that most of our resources should be diverted to neonatal units and the care of the very young. This would be to the detriment of all other departments. None of these things makes any real sense.

Let us assume that it has been decided that no patient older than 80 years of age should be treated with high-cost, life-saving technologies. The reason for doing so would presumably be to use the funds saved to treat younger patients (to enable them to have more years). But there is a problem that must be faced here by those who advocate ABR: if by not treating Mr. X, aged 83 years, the resource would instead be given to Miss H, aged 8 years, then there may be an argument for saying this should happen. But the numbers of those who are older than age 65 are increasing. So in fact what might be happening is that the funds saved by not treating Mr. X might be used to treat a patient who is in fact very little younger. The only way to justify such a policy (which is based on the fact that it is only potential life years that count in the allocation of resources) would be if it were stated that only those people who were very much younger would be treated, and that of course would be both absurd and unworkable, even if it were thought ethically supportable.

Conclusion

I have attempted to show that some of the reasons used to justify ABR, although superficially attractive, are flawed. At first sight it might seem sensible to suggest that the young should be given a chance to achieve a normal lifespan in preference to the "already old" extending theirs. However, this does not stand up to philosophical examination. The understandable feeling that it is somehow unfair that the elderly be given treatment that would reduce the resources available for the young may have an emotional appeal, but it cannot be justified in practice. I am not for one moment suggesting that the young should not be given every opportunity to become elderly, only that it should not be at the expense of the old. I have shown that there are many situations in which factors other than age are more important in deciding the allocation of funds and that being young is not in itself a quality that outweighs all other considerations in the allocation of scarce health care resources.

References

1. Callahan D. Setting limits. New York: Simon and Shuster, 1987.
2. Daniels N. Just health care. Cambridge: Cambridge University Press, 1985.
3. Shaw AB. In defence of ageism. J Med Ethics 1994; 20: 188–191.
4. Crisp R, Ebbs D, Hope T. The Asbury draft policy on ethical use of resources. Br Med J 1996; 312:1528–1530.
   Note that Crisp *et al.* (4) do not mention that many commentators have reservations about using QALYs (quality-adjusted life years) in such situations (or indeed any situations), nor do they give any of the many arguments against ABR. This is particularly interesting, because in the next paragraph of the article QALYs are rejected as a guide to the treatment of patients with chronic illness. It is surely reasonable to ask why Crisp et al. reject it for these patients but not elderly ones.
5. Mill JS. Utilitarianism, liberty, and representative government. London: JM Dent, 1964. Republished from earlier version: New York: EP Dutton, 1910.
6. Rawls J. Justice as fairness. Philos Rev 1958; 67:164–194.
7. Home Office Statistical Bulletin. Criminal careers of those born between 1953 and 1973. Research and Statistics Dept. 14/95. A publication of the Government Statistical Service. London, England: 1995.
8. Heller RF, Steele PL, Fisher JD, et al. Success of cardiopulmonary resuscitation after heart attack in hospital and outside hospital. Br Med J 1995; 311:1332–1336.
9. Foot P. Virtue and vices. Los Angeles: University of California Press; 1978.
10. Thomson JJ. The realm of rights. Cambridge: Harvard University Press, 1990.
11. Kappel K, Sandoe P. Saving the young before the old—a reply to John Harris. Bioethics 1994; 8(1):84–92.
    I assume that Kappel and Sandoe mean that the young have a presumption of a claim on resources, not that the young have a prior claim.
12. Lightfoot L, Rogers L. 'Dead' woman casts vote for right to stay alive. Sunday Times 7 Jan 1995; News Section, 3.
13. Callahan D. Setting limits: A response. Gerontologist 1994; 34:393–398.
14. Shakespeare W. Henry IV Part 2. Act III; scene 2.
15. Thomas D. Do not go gentle into that good night. In: Cohen J, Cohen J, eds. New Penguin book of quotations. London: Penguin, 1992: 426.

Research and/or Training on the Newly Dead:

The Jewish Perspective

Fred Rosner, M.D., F.A.C.P.

Using newly dead patients for medical research and other humanitarian and educational purposes has been proposed by numerous writers for more than two decades. In 1975, Gaylin suggested that the newly dead, which he called neomorts, could be used in the training of medical students to practice routine physical examinations, in the training of resident physicians to perform diagnostic procedures such as spinal taps and endotracheal intubation, for the testing of new drugs and surgical procedures, for the harvesting and banking of a variety of tissues and organs, and for the manufacture of antibodies and hormones (1). He concluded, however, that the recycling of human bodies would evoke repugnance because of the "inhumanity" of it all.

In 1980, Casado de Frias et al. (2) experimentally injected lithium into a brain-dead child and measured the secretion of antidiuretic hormone. In an accompanying editorial, Fost (3) stated that such research should be "permissible when an important social purpose is being served, when consent from a suitable guardian is obtained, and when the invasion is done in a way that seeks to avoid desecration and preserves respect for the human form." Also in 1980, Robertson (4) pointed out that research on brain-dead people is not subject to or covered by governmental rules that regulate Institutional Research Review Boards (IRBs) but should be approved as long as surviving kin's consent is obtained and any other applicable guidelines followed. Serious reservations, however, are expressed by Smith in an accompanying commentary (5). Martyn (6) suggests that IRB regulations should be amended to require review of proposed research on the newly dead which will benefit both the scientific community and affected individuals.

Drawing heavily on May's arguments about moral sensibility, sentimentality, and squeamishness to disallow the routine "harvesting of the dead" (7), Feinberg (8) disagreed and found "no unmanageable conflict between effective humanitarianism and the maintenance, under flexible control, of the essential human sentiments." Cadavers offer a more realistic training opportunity than mannekins for such procedures as endotracheal intubation, lumbar puncture, and bone narrow aspiration (9). If such teaching is done on the newly dead in a respectful and compassionate atmosphere, no ethical objections exist according to some authors (9, 10) who have claimed that "there is neither a legal nor a moral basis for requiring relatives' consent for minimally invasive and non-invasive postmortem procedures" (11). Most authors, however, required prior consent of the parties concerned (12–14). Some writers proposed that consent be presumed in the absence of a specific advance directive to the contrary (15). Some authors were opposed to using the newly dead to help the living because of possible misperceptions of death and altered human sensibilities (16).

A recent national survey of emergency departments revealed that endotracheal intubation on recently deceased patients is taught in more than half the responding hospitals, often without

---

Director of Medicine, Mount Sinai Services at Queens Hospital Center and Professor of Medicine, Mount Sinai School of Medicine. Address correspondence and reprint requests to Fred Rosner, M.D., F.A.C.P., Queens Hospital Center, 82-68 164 Street, Jamaica, NY 11432.

the patients or their families being informed about this practice (17). Consent is also rarely obtained for the cannulation of a central vein in adult patients on whom cardiopulmonary resuscitation has been unsuccessful (18). Yet, the majority of families of newly dead infants (19) or adults (20) will consent to them being intubated for teaching purposes.

In 1988, Coller et al. (21) studied a monoclonal antibody's inhibition of human platelet function in a newly dead 78-year-old man with approval of the university's IRB and the patient's next of kin. The ethical issues in this experiment were discussed in detail by Coller elsewhere (13) where he enunciated 10 principles that should govern such research. Other legal (6) and ethical (3–5, 22) concerns about research on the newly dead have been expressed by many authors. This essay is devoted to the Jewish religious view of the use of the newly dead for training purposes or for medical research.

The Jewish View Regarding the Practice of Medicine

Judaism is guided by the axioms of the supreme sanctity of human life and the dignity of man created in the image of God. The preservation of human life in Judaism is a divine commandment. To save a life, all religious laws are automatically suspended, the only exceptions being idolatry, murder, and forbidden sexual relations such as incest or adultery. The value of human life is infinite. The bodies and souls of human beings are gifts from God. People do not possess absolute title over their lives or bodies. They are like stewards charged with preserving and dignifying their life. It is therefore required that we follow a regimen of life to maintain our health. Jews must eat and drink properly and not excessively, exercise regularly, sleep adequately, only engage in proper and legitimate sexual activities, and lead an overall healthy life-style. These are moral obligations and legal imperatives in Judaism.

These and other general principles of Jewish medical ethics have been detailed in several monographs (23–30). What is the Jewish attitude toward the dead? Is nonmutilating use of the newly dead for teaching residents permitted or forbidden? Is it considered "deriving benefit" from the dead, which is forbidden in Jewish Law? Is it permissible to delay burial for this teaching purpose to be accomplished? In most religions, including Judaism, the physical remains of a deceased person must be treated with honor and respect. Judaism requires not only that the dead be treated with utmost dignity and honor but that no desecration of the dead be performed except where such an act may immediately save a life. Even in such a situation, all organs examined and/or removed must be returned to the body before burial. Burial must not be delayed. No benefit may be derived from the dead except where a life is at stake. Several of these issues relate directly to the ethical question as to whether or not the newly dead can be used for medical research or training purposes. The following discussion will show that Judaism sanctions the nonmutilating use of the newly dead for teaching purposes and does not consider if forbidden as deriving benefit from the dead nor as an unnecessary delay in the requirement for prompt burial of the dead.

Desecration of the Dead

The prohibition of desecrating or disgracing the dead is based on the biblical passage,

> And if a man has committed a sin worthy of death, and he be put to death, and thou hang him on a tree, his body shall not remain all night upon the tree but thou shalt surely bury him the same day (31).

The Talmud interprets this phrase to mean that just as hanging all night is a disgrace to the human body, so too any action which constitutes a disgrace to the deceased is prohibited (32). If the Torah is concerned for the body of a convicted criminal, then all the more certainly, the body of a law-abiding citizen should be treated with the proper respect and be interred without being subjected to shame or disgrace.

Two talmudic passages dealing with postmortem examination are relevant, although neither deals directly with dissection of the dead for purely medical purposes. One case deals with criminal law, the other with civil law. The first case deals with a murderer for whom the Divine Law prescribes death. The Talmud asks:

> Why do we not fear that the victim may have been afflicted with a fatal organic disease, for whose killing a person is not punishable as a murderer? Is it not because we follow the majority, and most victims of murderers are not so afflicted? And should you say that we can examine the body—this is not allowed because it would thereby be mutilated. And should you say that since a man's life [the accused] is at stake, we should mutilate the body, then one could answer that there is always the possibility that the murderer may have killed the victim by striking him in a place where he was suffering from a fatal wound, thus removing all traces of the wound. In such a case, it is clear that no amount of postmortem examination would show that the victim was afflicted with a fatal disease (33).

Therefore, it is proved, concludes the Talmud, that we follow the majority and do not perform an autopsy. In this case, the findings of an autopsy, even if it were permitted, would have been irrelevant to the conviction of the murderer and insufficient to acquit him.

The second case is the story told in Bene-Berak that a person once sold his father's estate and died (34). The members of the family protested that he was a minor at the time of his death and, therefore, not eligible to sell any of his father's estate. Hence, the property he sold should belong to the surviving members of the family. They came to Rabbi Akiva and asked whether the body might be exhumed and examined to ascertain the age of the deceased by performing a postmortem examination. Rabbi Akiva replied that one is not permitted to dishonor the dead by disinterment; and, furthermore, the signs of maturity usually undergo a change after death. Hence, the examination would not produce reliable evidence of his age.

Neither talmudic case deals with postmortem desecration for medical purposes, but both illustrate the objection to this procedure on the grounds that it would constitute a desecration of the dead, a biblically prohibited act.

Does the use of the newly dead for the training of residents and emergency medical technicians in endotracheal intubation constitute a desecration of the dead in Jewish law? The answer is no, because no incision or mutilating procedure is performed. A visible incision into the body or the removal of externally visible or internal organs represent true desecrations and are only permitted for the immediate saving of the life of an extant patient. Thus, organ transplants are permissible to save the lives of patients dying of organ failure, provided the donor is dead at the time the organ is removed for transplantation (25–27, 29–30). The use of the newly dead for medical research or training that does not involve incisions in the body does not, therefore, violate the biblical prohibition against desecrating the dead. This thesis is supported unabiguously by Rabbi Moshe Feinstein in a rabbinic responsum dealing with autopsy (35). Feinstein states that if the organs are not removed and the neck and abdomen are not opened, but the physicians want only to insert a needle to remove some liquid from which to learn about the illness, this is not considered a desecration of the dead because such procedures are done nowadays to the living and are certainly allowed. Similarly, to remove a little blood or similar substance (tissue) with a needle is not a desecration and it is permissible. So too, postmortem laparoscopy or peritoneoscopy to confirm a diagnosis is also not forbidden because there is no desecration involved.

Deriving Benefit from the Dead

Based on a talmudic discussion (36), the major codes of Jewish law of Moses Maimonides (1138–1204) (37) and Joseph Karo (1488–1575) (38) rule that the Bible prohibits one from deriving benefit from the dead. This prohibition, according to Rabbi Jacob Emden (1697–1776), is only rabbinic (rather than biblical) in nature, and may be waived for medical treatment (39). However, most Rabbis consider deriving benefit from the dead to be a biblical prohibition which can only be waived for the immediate saving of a human life.

Rabbi Zvi Pesach Frank (1873–1960), former Chief Rabbi of Jerusalem, states that looking at the body for the sake of studying anatomy or even dissecting the body to enhance general knowledge is considered to be an indirect use of the body and, therefore, not prohibited (40). He cites Rabbi Solomon Adret (1235–1310), known as *Rashba,* who asserts that the prohibition of deriving benefit from the dead applies only if one directly benefits from the dead, such as selling the body for monetary gain. However, if the benefit is indirect, there is no prohibition. Rabbi Shlomo Zalman Auerbach (1910–1995) is quoted (41) as allowing intubation of the dead for the sake of training doctors and technicians to save lives in the future.

Rabbi David ben Zimra (1479–1598), known as *Radvaz,* states that even if the prohibition is biblical in origin, only conventional uses of the cadaver are prohibited (42). Other Rabbis disagree. Most Rabbis, however (see above), rule that there is no prohibited benefit involved in using bodies for the sake of research or medical training, because the benefit is derived indirectly, because the body does not provide the benefit but is the source of the benefit, which derives by itself and is therefore not prohibited. Learning from the body is not considered as deriving a benefit because the benefit is not derived by using the body for medical research or for teaching purposes but from the understanding that flows or the information gained from this activity (43). Some Rabbis write that for the sake of studying medicine, the prohibition of deriving benefit from the dead does not apply because one thereby fulfills the commandment of healing the sick and commandments are not meant to impart benefit to those who fulfill them (44). These are technical points of Jewish law.

It thus seems that there is a substantial body of rabbinic opinion which would not consider the use of the newly dead for medical research or medical teaching to constitute a violation of the prohibition against deriving benefit from the dead, because the researchers and teachers are not directly and personally benefitting.

Prompt Burial of the Dead

In Judaism, the obligation to promptly bury the dead is based on the positive commandment, "Thou shalt surely bury him" (45). If one unnecessarily delays the burial of the deceased, one transgresses the negative precept of "His body shall not remain all night" (45). Does the use of a body for medical research or for training of intubation skills constitute an improper delay in the burial of the deceased? The Talmud indicates that the obligation to bury the dead immediately after death is set aside if more time is needed to accord proper honor to the deceased (46). Funeral arrangements may take hours or sometimes longer. The Jewish issue is that delay might demonstrate a lack of concern for the dignity of the body. Therefore, if the delay is intended to enhance the dignity and honor of the deceased, it is permitted. The Bible gives many examples of delaying funerals for various reasons including the funerals of Sarah (47), Jacob (48) and the sons of King Saul (49). If it is a true honor for the deceased to postpone the funeral, such as waiting for the next of kin to arrive, it is permitted (50). Hence, a brief interval after death for medical training or medical research might not constitute any violation of the biblical commandment requiring prompt burial of the dead.

Discussion

The Talmud compares a deceased human being to a Scroll of the law [Sefer Torah (51)] and says that a dead body must be treated with dignity and respect (52). He who treats a dead body with disrespect transgresses a biblical commandment (53). The deceased must be buried promptly, including all organs or parts that might have been removed for whatever reason. Cremation is not permitted in Judaism. Desecrating the dead, deriving benefit from the dead, and delaying or not burying the dead are all biblical prohibitions.

Because Judaism teaches that man is created in the image of God, every dignity must be extended to the human body in death as in life. It is for this reason that the body must be regarded as inviolate. Except in certain very limited circumstances, Jewish law does not sanction the performance of autopsies. It is, however, the consensus of rabbinic opinion that postmortem examinations may be performed for the purpose of gaining specific information of immediate benefit in the treatment of other patients already afflicted by a life-threatening disease. A case in point is a person with cancer who died after receiving an experimental drug or drug combination. Postmortem examination to ascertain possible toxicity, foreboding potential harm to other patients on the same course of treatment, or for purposes of obtaining information concerning the therapeutic efficacy of the drug or drug combination, would be warranted according to Jewish law when such information is deemed to be essential in the treatment of other patients already suffering from the same illness.

Another instance in which autopsy is not only allowed but probably mandated is the situation of life-threatening infectious disease, such as Legionnaire's disease. At a convention in Philadelphia in 1976, several hundred Legionnaires were afflicted with a pneumonia-like illness and many died. Jewish law would probably dictate autopsy on those who died to discover the offending organism (now known) and treatment (now available) to save the lives of the other patients afflicted, many of whom were dying of the same illness.

The dominant consideration in permitting an autopsy is the immediacy of the constructive application of the findings. This "here and now" principle, once limited to the medical needs of a local community, can now be extended, through the excellence of communications and scientific reporting, to the whole medical world. Results of autopsies in New York can be available in London in a matter of minutes. However, a routine autopsy cannot be sanctioned, although great benefit may accrue at some distant future time (23, 25, 26, 29).

The use of the newly dead for medical research or medical education without anatomical dissection of the deceased seems to be permissible in Judaism. No prohibited desecration or mutilation of the body is involved. The prohibition against deriving benefit from the dead is not violated because the benefit is indirect. Prompt burial can still be arranged and no forbidden delay in funeral arrangement occurs if the research or medical training lasts only minutes or at most a few hours.

Whether or not permission is needed from the deceased or the next of kin is debated among the Rabbis. Some require permission because people have certain rights over their body including the right to decide what shall and what shall not be done. Other Rabbis state that we do not own our bodies because they are given to us on loan by God and we serve as stewards over them. Therefore, Jewish society can decide that such permission is not required when the health and welfare of its citizens are at stake, because society has the communal obligation to provide health care including the search for cures of illnesses and training of medical personnel. Judaism also espouses the principle that "the law of the land is the law." Hence, if American law requires informed consent for medical research or training on the newly dead, Jewish law requires that law to be obeyed.

Acknowledgments

The author is indebted to Rabbi David Bleich, Rabbi Tzvi Flaum, and Rabbi Moshe D. Tendler for helpful suggestions.

References

1. Gaylin W. Harvesting the dead. The potential for recycling human bodies. Harpers Sept 1974: 23–30.
2. Casado de Frias E, Balboa de Paz F, Perez Martinez A, Palacio Mestres C. Inappropriate secretion of antidiuretic hormone and the effect of lithium in its treatment. J Pediatr 1980; 96:153–155.
3. Fost N. Research on the brain dead. J Pediatr 1980; 96: 54–56.
4. Robertson JA. Research on the brain dead. IRB 1980; 2: 4–6.
5. Smith DH. On being queasy. IRB 1980; 2:6–7.
6. Martyn SR. Using the brain dead for medical research. Utah Law Rev 1986; 1:11–28.
7. May W. Attitudes toward the newly dead. Hastings Cent Studies 1972; 1:3–13.
8. Feinberg J. The mistreatment of dead bodies. Hastings Cent Rep 1985; 15(Feb):31–37.
9. Brattebo G, Seim SH. Teaching training of invasive procedures on cadavers. Lancet 1988; 2:1078–1079.
10. Iverson KV. Requiring consent to practice and teach using the recently dead. J Emerg Med 1991; 9:509–510.
11. Iverson KV. Postmortem procedures in the emergency department: using the recently dead to practice and teach. J Med Ethics 1993; 119:92–98.
12. Culver CM. Using a cadaver to practice and teach. Hastings Cent Rep 1986; 16(June):28–29.
13. Coller BS. The newly dead as research subjects. Clin Res 1989; 37:487–494.
14. Burns JP, Reardon FE, Truog RD. Using newly deceased patients to teach resuscitation procedures. N Engl J Med 1994; 331:1652–1655.
15. Orlowski JP, Kanoti GA, Mehlman MJ. The ethics of using newly dead patients for teaching practicing intubation techniques. N Engl J Med 1988; 319:439–441.
16. Trainor R. Should the newly dead be used to help the living? An issue in our time. Linacre Q 1989; 56:51–63.
17. Morhaim DK, Heller MB. The practice of teaching endotracheal intubation on recently deceased patients. J Emerg Med 1991; 9:515–518.
18. Tachakra SS, Robinson SM, Mitchell M. Teaching intubation skills using newly deceased infants. JAMA 1991; 266:1649–1650.
19. Benfield DG, Flaksman RJ, Lin TH, Kantak AD, Kokomoor FW, Vollman JH. Teaching intubation skills using newly deceased infants. JAMA 1991; 265:2360–2363.
20. McNamara RM, Monti S, Kelly JJ. Requesting consent for an invasive procedure in newly deceased adults. JAMA 1995; 273:310–312.
21. Coller BS, Cudder LE, Berger HJ, Iulliucci JD. Inhibition of human platelet function in vivo with a monoclonal antibody with observations on the newly dead as experimental subjects. Ann Intern Med 1988; 109:635–638.
22. LaPuma J. Discovery and disquiet: research on the brain-dead. Ann Intern Med 1988; 109:606–608.
23. Jakobovits I. Jewish medical ethics. New York: Bloch, 1959.
24. Feldman DM. Birth control in Jewish law. New York: New York University Press, 1968.
25. Rosner F, Bleich JD. Jewish bioethics. New York: Sanhedrin Press, 1979.
26. Feldman DM, Rosner F. Compendium on medical ethics, 6th ed. New York: Federation of Jewish Philanthropies, 1984.
27. Bleich JD. Judaism and healing. Hoboken, NJ: Ktav and Yeshiva University Press, 1981.
28. Meier L. Jewish values in bioethics. New York: Human Sciences Press, 1986.
29. Rosner F. Modern medicine and Jewish ethics, 2nd ed. Hoboken, NJ and New York, NY: Ktav and Yeshiva University Press, 1991.
30. Feldman DM. Health and Medicine in the Jewish Tradition, New York, Crossroad Publ. 1986.
31. Deuteronomy 21:22–23.
32. Sanhedrin 47a.
33. Chullin 11b.
34. Baba Bathra 154a.
35. Feinstein M. Responsa Iggrot Moshe, Yoreh Deah, Part 2 No. 152, New York, 1973.
36. Abodah Zara 29b.
37. Maimonides M. Mishneh Torah, Avel 14. Vilna: Rosencrantz, 1900.
38. Karo J. Shulchan Aruch, Yoreh Deah 349. Vilna: Romm, 1911.
39. Emden J. Responsa Sheelat Yavetz, Part 1 No. 41, Altona, 1739.
40. Frank ZP. Responsa Har Zvi, Yoreh Deah No. 278, Jerusalem, 1950.
41. Abraham AS. Nishmat Abraham, Yoreh Deah 349:2, Jerusalem, 1993.
42. David ben Zimra. Responsa Radvaz, Part 3 No. 548, Warsaw, 1882.
43. Steinberg A. Encyclopedia of Jewish medical ethics. vol. 4, pp. 559–562. Jerusalem, 1994.
44. Breisch M. Responsa Chelkat Yaakov, Part 1 No. 84, Zurich, 1963.
45. Deuteronomy 21:23.
46. Sanhedrin 46a.
47. See Sanhedrin 46b.
48. Genesis 50:2.
49. 2 Samuel 21:10.
50. Feinstein M. Responsa Iggrot Moshe, Yoreh Deah No. 139, New York, 1959.
51. Shabbat 105b and Moed Katan 25a.
52. Berachot 18a.
53. Sanhedrin 26b.

Asymptomatic Hepatopathy Is Frequent in Chronic Alcoholic Pancreatitis

Júlio Maria Fonseca Chebli, M.D., Edson Lobo, M.D., Valéria Pereira Lanzoni, M.D., and Manoel Martins Das Neves, M.D.†

Abstract

Background: Chronic ethanol abuse is a common cause of chronic hepatic and pancreatic diseases in Western countries. The objectives of the present study were to determine the occurrence and the clinical evolution during follow-up of asymptomatic hepatic disease in Brazilian alcoholics with chronic pancreatitis whose most important beverage is *cachaça,* a beverage distilled from sugar cane.

Patients-Methods: Thirty-two patients, mean age 35 years, with a mean daily ethanol intake of 204 g during a mean period of 16 years, presenting with chronic pancreatitis without clinical and laboratory features of hepatocellular failure, were followed up during 34 ± 8 months after undergoing a percutaneous biopsy of the liver and histological examination.

Results: Hepatic injury was observed in 50% of the cases. During the follow-up, only one patient showed clinical or biochemical evidence of hepatic deterioration or complication.

Conclusions: In subjects with a chronic intake of *cachaça,* the association between asymptomatic alcoholic hepatopathy and chronic alcoholic pancreatitis is frequent (50%). In chronic alcoholic pancreatitis, associated hepatic disease may remain asymptomatic in the majority of the cases and has little influence on the outcome of the patients, at least in a short-term follow-up.

PRACTICALLY ALL THE ORGANS and systems of the organism are vulnerable to the toxic effects of ethanol and its metabolites. In the gastrointestinal system, the organs most affected are the pancreas and the liver. Only some alcoholics, however, develop hepatic and/or pancreatic disease, which suggests that other factors (genetic, nutritional, hormonal, and environmental) may also influence the pathogenesis of these diseases (1).

The hepatic damage that occurs in the chronic alcoholic pancreatitis (CAP) can occur as a consequence of the direct toxic effect of ethanol and of the pancreatic disease itself (2). The occurrence and the type of alcoholic hepatic disease (AHD) associated with pancreatopathy is variable (2), depending on the type of study conducted and the criteria used to diagnose the hepatopathy.

The frequency and even the severity of the hepatic lesions associated with CAP tend to be greater in necropsy data (3, 4). On the other hand, when only clinically significant manifestations are considered, the rate of hepatopathy in individuals suffering from pancreatitis is low (5–7).

Clinical and laboratory alterations are not entirely reliable for the diagnosis of AHD in individuals with chronic pancreatitis (8–10). The gold standard, in these cases, is the histopathological study of the liver (11). Even considering the latter point, several studies have shown differing results regarding the association of AHD in CAP (2, 12–14).

The knowledge of the morphofunctional hepatic state in CAP is very important, because it

---

†Deceased

Study supported in part by CAPES-Brazil.

Address reprint requests to Dr. Júlio Maria Fonseca Chebli, Rua Vieira Pena, 287 Juiz de Fora-MG CEP: 36026-300, Brazil.

TABLE 1
Clinical Findings in Chronic Alcoholic Pancreatitis

Clinical findings[a]	n	%
Recurrent chronic pancreatitis without any other aspects	18	56
Internal pancreatic fistula (pleural effusion)	5	16
Pseudocyst	11	34
Pancreatic calcifications	4	12
Steatorrhea	2	6

[a] A few patients had more than one clinical finding.

will allow better clinical management, especially for the more appropriate preparation of these patients when surgical intervention resulting from complications of the pancreatic disease is considered. Without recognizing the associated hepatic pathology, which may not be apparent, complications resulting from the surgical procedure itself may arise and aggravate the clinical course in this situation.

In view of the possible importance of any associated hepatic disease in patients with CAP and the lack of information on its clinical course, we assessed its presence and clinical outcome. In Brazilian patients (whose most important beverage is *cachaça*, a beverage distilled from sugar cane) with CAP, there was no clinical or laboratory evidence to suggest hepatocellular failure.

Patients and Methods

Thirty-two male patients admitted to the Gastroenterology Ward of the Hospital São Paulo, Escola Paulista de Medicina, São Paulo, Brazil, were evaluated between January 1991 and November 1992. These patients suffered from CAP, and their diagnosis was based on a combination of criteria: clinical, recurrent abdominal pain and/or steatorrhea; biochemical, hyperamylasemia more than three times the upper limit of normal, or with a higher concentration of amylase in the pleural or peritoneal liquid than the concentration in serum; and computed tomography scans and alterations in the endoscopic retrograde cholangiopancreatography that suggested a chronic pancreatic disease (**Table 1**). None of the patients presented any previous diagnosis of hepatopathy or any clinical aspects (jaundice, spiders, palmar erythema, ascites, hepatic encephalopathy) or laboratory indications (prolonged prothrombin time, hyperbilirubinemia, hypoalbuminemia) suggestive of hepatic failure.

The exclusion criteria were: cholelithiasis, hypertriglyceridemia, a family history of pancreatitis, use of drugs related to pancreatitis, use of hepatotoxic medications, recreational drug abuse, and diabetes mellitus.

The patients' mean age was 35 years (range, 19–58 years), with an average ethanol intake of 204 g/day (range, 80–750 g) in the guise of *cachaça* for an average period of 16 years (range, 6–38 years). All maintained their ethanol intake until the eve of being admitted to hospital.

During the patients' stay at the hospital, an abdominal computed tomography scan and endoscopic retrograde cholangiopancreatography were performed. Alterations in serum chemistry were used to evaluate the presence of pancreatic disease. Viral markers of hepatitis (hepatitis B surface antigen [HBsAg], enzyme-linked immunosorbent assay [ELISA], Abbott Laboratories, North Chicago, IL; anti-hepatitis C virus [HCV] 2nd generation ELISA, Abbott Laboratories), antinuclear antibody and smooth muscle antibody (indirect immunofluorescence) were also performed. The liver biopsy was performed after the regression of the current clinical picture of pancreatic inflammation ($n = 24$), in the case of surgical indication ($n = 6$) or immediately after death ($n = 2$) using a Tru-cut biopsy needle (Allegiance Healthcare, McGaw, IL). The coagulation studies were appropriate for the liver biopsy (prothrombin time within 2 seconds of the patient's control and platelet count above 150,000 mm^3). No complications of the procedure were observed.

The fragments of the liver tissue were fixed in buffered neutral formol saline and embedded in paraffin wax. Tissue sections (2 μm) were routinely stained with hematoxylin and eosin, Masson's trichrome, Gordon and Sweet's reticulina, emphasizing the morphological features recognized to be associated with ethanol toxicity (11). In addition, the sections were stained for hepatitis B core antigen (HBcAg) by the peroxidase-antiperoxidase method of Sternberger et al. (15). The primary antibody used for staining was rabbit anti-HBcAg purchased from Dako Laboratories (Santa Barbara, CA). Secondary antibody was swine anti-rabbit IgG (Dako Laboratories). Each fragment contained at least three well-defined portal spaces. The biopsies were examined by two independent pathologists unaware of the patient's clinical details who later compared their results to arrive at a combined decision on each case. Any of the following histologic findings were considered significant for AHD: marked perivenular fibrosis, alcoholic hepatitis, active chronic hepatitis, or cirrhosis (2, 11).

To verify the onset, or not, of the features suggesting aggravation or complications of associated hepatic disease during outpatient's follow-up, clinical and biochemical evaluation, as well as, abdominal ultrasound were routinely performed at intervals of at least 6 months. The onset of jaundice, ascites, hepatic encephalopathy, prolonged prothrombin time (>2 seconds of the patient's control), or gastrointestinal bleeding caused by rupture of esophageal varices were considered to be evidence of hepatic deterioration.

The written informed consent of all the patients was obtained and the study was approved by the Commission on Medical Ethics of the Escola Paulista de Medicina, São Paulo, Brazil.

TABLE 2
Hepatic Histology in Patients with Chronic Alcoholic Pancreatitis

Principal histologic diagnosis	n	%
Marked perivenular fibrosis (with or without steatosis)[a]	7	22
Alcoholic hepatitis[a]	5	16
Active chronic hepatitis[a]	2	6
Micronodular cirrhosis[a]	2	6
Mild steatosis	6	19
Extrahepatic cholestasis	4	12
Normal liver	6	19
Total	32	100

[a] Significant alcoholic hepatic disease.

Results

Table 2 shows the findings of the hepatic histology in the group of individuals suffering from chronic pancreatitis. It was observed that in 16 cases (50%) there was some form of significant AHD. We emphasize that we did not consider the finding of mild steatosis a significant AHD.

Regarding viral hepatitis markers, a single patient was HBsAg positive, but hepatitis B e antigen (HBEAg) negative. The results of the search for HBcAg in the tissue and for serum HCV antibodies were negative in all cases. In the two cases of active chronic hepatitis the search for the antinuclear antibody and the smooth muscle antibody were negative. Serum levels of ceruloplasmin, copper, and α_2-antitrypsin were normal.

During the follow-up of these patients for 34 ± 8 months, 10 were operated on for complications of chronic pancreatitis (2 pancreatic resections, 5 pancreaticojejunostomies, and drainage of three pseudocysts). Of these, 6 had AHD as shown in a previous biopsy (marked perivenular fibrosis in 3, alcoholic hepatitis in 2, and active chronic hepatitis in 1). None of these patients had any complications of underlying AHD. In the other 20 patients, 10 had associated AHD as shown in previous biopsy (cirrhosis in 2, active chronic hepatitis in 1, alcoholic hepatitis in 3, and marked perivenular fibrosis in 4). Only one patient of this group (with hepatic cirrhosis) developed evidence of hepatic complication (ascites) during follow-up.

Discussion

In the present study, the association of significant AHD (alcoholic hepatitis, active chronic hepatitis, intense perivenular fibrosis, and hepatic cirrhosis) and CAP was 50%, even considering the fact that the patients with previously diagnosed hepatopathy had been excluded, approximating the findings of some studies (2, 16) but not of others (12–14). Nevertheless, none of the patients had jaundice or any other clinical signs of hepatocellular failure.

In this study, 16% of the patients who presented with AHD suffered from alcoholic hepatitis, which agrees with previous studies (16, 17). None of the patients were either obese or diabetic, conditions that simulate the histology of alcoholic hepatitis (18).

The presence of active chronic hepatitis in two patients probably resulted from the effect of ethanol, as described previously (19). In both cases we excluded, to the best of our abilities, other etiologies of this type of hepatic lesion such as infection by B and C viruses, autoimmune hepatitis, drugs, and Wilson's disease. Most cases of chronic hepatitis in alcoholics are caused by HCV (20).

A typical lesion of alcoholic injury, marked perivenular fibrosis, was found in 22% of the cases. Its importance lies in the fact that individuals with perivenular fibrosis, even in the stage of a fatty liver, have a greater probability of progressing quickly to more serious stages of alcoholic hepatopathy if the consumption of ethanol persists (21).

The occurrence of hepatic cirrhosis in this study (6%) is close to that reported by other authors (10, 17, 22). In practice, this association is certain to be higher, in view of the fact that in this study we excluded patients with clinical or laboratory aspects that suggested any hepatocellular failure, who would be more likely to present with hepatic cirrhosis. Another possibility is that the length of our patients' period of ethanol intake (16 ± 8 years) was not long enough to determine the occurrence of cirrhosis in a greater number of cases, which agrees with the findings of Durbec and Sarles (23), who demonstrated the beginnings of the symptoms of cirrhosis, on average, after 29.9 ± 10.5 years of regular ethanol consumption, whereas, for CAP, this period was 18 ± 11 years. The frequent presence in this group of hepatic lesions which we know to be the precursors of cirrhosis, such as alcoholic hepatitis, perivenular fibrosis, and active chronic hepatitis, would provide additional support to this possibility. Thus, if these patients maintain their ethanol intake, several of them may develop hepatic cirrhosis.

The duration of the intake of ethanol is probably not the only determinant of greater or lesser frequency of cirrhosis with CAP. There may be individual sensibility, preferential or increased, of the pancreas or of the liver to alcoholic damage, as suggested previously (14, 23).

The presence of steatorrhea and/or pancreatic calcifications, which usually denote a later phase of the pancreatic disease (24), occurred in 18% of the cases. In none of these was hepatic cirrhosis, the most advanced form of AHD, found in the histology. This observation supports previous reports (17, 19) that did not observe any relationship between the degree of involvement of the pancreas and the liver in patients with a coexistence of CAP and AHD. In other words, the lesions of both organs caused by ethanol would develop independently and, very likely, at different times.

Extrahepatic cholestasis was present in 12% of the cases without jaundice and was found to be caused by impaired common bile duct function with the pancreatic inflammation and fibrosis. We emphasize that the liver was normal or presented nonspecific histological alterations in only six cases.

In these patients viral infection did not participate in the hepatic lesions observed. In all patients the serum antibodies to HCV and the search for tissue HBcAg were negative. However, in one case HBsAg was positive and there was mild steatosis in the biopsy. The serum was negative for HBeAg.

The prevalence of HCV antibodies in patients with AHD, mainly in those with advanced hepatic disease, has increased (25). In a multicenter trial, antibody to HCV correlated significantly with clinical severity of the disease and with the presence of histological features that imply chronic viral infection (periportal inflammation, cirrhosis) (25). On the other hand, when patients with AHD who have a history of intravenous drug use are excluded, the rate of HCV antibody reactivity is found to be the same as that found in the general population (26). In another study, anti-HCV seropositivity was strongly associated with histological findings of chronic hepatitis (portal and/or lobular inflammation) in alcoholic patients. In contrast, HCV antibodies were detected in only 16% of patients without portal and/or lobular hepatitis. Furthermore, these histological findings were also correlated with a history of intravenous drug use (20). In accordance with the above-mentioned reports, the absence of HCV antibodies in our series may be related to the exclusion of patients with a history of intravenous drug use as well as the low incidence of cirrhosis (6%) and chronic hepatitis (6%). Nevertheless, the absence of viral markers of hepatitis in CAP patients with liver pathology observed in this study, although interesting, is based on a very small sample of patients and cannot be generalized.

The remarkable absence of clinical and biochemical features of hepatocellular failure in this group of heavy drinkers with CAP stands in sharp contrast to the morphological findings associated with alcohol-induced liver injury observed in 50% of the patients. Nevertheless, during follow-up of 30 patients for 34 ± 8 months (16 with AHD in previous biopsy), deterioration or complications of hepatic disease was a rare event occurring in only one case (6%).

Although alcohol consumption is notoriously difficult to quantify (27), we have hypothesized that during the follow-up interval ethanol intake might have decreased as a result of counselling as well as the risk of pain and possible surgery because of recurrent pancreatitis. The tendency to hepatic deterioration which might have followed a maintained level of ethanol intake might thus have been decreased.

The findings of this study probably reflect the incidence of asymptomatic AHD in patients with more advanced CAP. We did not evaluate patients with minimal pancreatic dysfunction (28) or those with asymptomatic CAP. The results of this study suggest that although asymptomatic AHD (normal clinical and biochemical findings) may exist in patients with CAP, in the short term, hepatic disease does not seem to be aggravated and it does not influence the clinical outcome. Longer follow-up and many more patients will be necessary to confirm the interpretation of the results of this study.

References

1. Mezey E, Kolman CJ, Diehl AM, Mitchell MC, Herlong HF. Alcohol and dietary intake in the development of chronic pancreatitis and liver disease in alcoholism. Am J Clin Nutr 1988; 48:148–151.
2. Dutta SK, Mobrahan S, Iber Fl. Associated liver disease in alcoholic pancreatitis. Dig Dis 1978; 23:618–622.

3. Clark E. Pancreatitis in acute chronic alcoholism . Am J Dis 1942; 9:428–431.
4. Mincis M, Barollo CR, Filho BH, Saad FA. Hepatic and pancreatic alterations in chronic alcoholics. Rev Assoc Med Bras 1973; 19:365–370.
5. Sarles H, Sarles JC, Camattle R, Muratore R, Gaini M. Observations on 205 confirmed cases of acute pancreatitis, recurring pancreatitis and chronic pancreatitis. Gut 1965; 6:545–559.
6. Marks IN, Girdwood AH, Bank S, Louw JH. The prognosis of alcohol-induced calcific pancreatitis. S Afr Med J 1980; 57:640–645.
7. Ammann RW, Hammer B, Fumagalli I. Chronic pancreatitis in Zurich, 1963-1972. Clinical findings and follow-up studies of 102 cases. Digestion 1973; 9:404–410.
8. Reynolds TE, Hidemura R, Michel H, Peters R. Portal hypertension without cirrhosis in alcoholic liver disease. Ann Intern Med 1969; 70:497–500.
9. Macquart-Moulin G, Cornee J, Lauret F, Sarles H. Jaundice and chronic pancreatitis. Digestion 1980; 20:410.
10. Dani R, Nogueira CED, Riberio M, Nunes A. Concomitance of hepatic lesions in calcifying alcoholic pancreatitis. Study of 60 cases. Arq Gastroenterol 1983; 20: 103–107.
11. Saunders JB. Alcoholic liver disease in the 1980s. Br Med J 1983; 287:1819–1821.
12. Barros MIB, Ohki Y, Mott CB, Machado MCC, Betarello A. Functional and structural evaluation of the liver in chronic alcoholic pancreatitis. Arq Gastroenterol 1973; 19:251–256.
13. Wilson C, Auld CD, Sclkinkert R, et al. Hepatobiliary complications in chronic pancreatitis. Gut 1989; 30: 520–527.
14. Jalleh RP, Gilbertson JA, Williamson RCN, Foster CS. Morphological and immunohistochemical analysis of the human liver in chronic pancreatitis. Gut 1991; 32: 1386–1391.
15. Sternberger LA, Hardy PH Jr, Cuculis JJ, et al. The unlabeled antibody enzyme method of immunohistochemistry: preparation and properties of soluble antigen-antibody complex (horseradish peroxidase-antihorseradish peroxidase) and its use in identification of spirochetes. J Histochem Cytochem 1970; 18:315–333.
16. Angelini G, Merigo F, Degani G, et al. Association of chronic alcoholic liver and pancreatic disease: A prospective study. Am J Gastroenterol 1985; 80:998–1003.
17. Morl M, Piechulekh. Lebershaden bei chronhisch-Kalzifizieter, alkoholin-duzieter panckreatitis. Z Gastroenterol 1987; 25:325–330.
18. Ludwig J, Viggiano TR, Megill DB. Nonalcoholic steatohepatitis: Mayo Clinic experience with a hitherto unnamed disease. Mayo Clin Proc 1980; 55:434–438.
19. Takase S, Takada N, Enomoto N, Yashuhara M, Takada A. Different types of chronic hepatitis in alcoholic patients. Does chronic hepatitis induced by alcohol exist? Hepatology 1991; 13:876–881.
20. Rosman AS, Paronetto F, Galvin K, Williams RJ, Lieber CS. Hepatitis C virus antibody in alcoholic patients: Association with the presence of portal and/or lobular hepatitis. Arch Intern Med 1993; 153:965–969.
21. Worner TM, Lieber CS. Perivenular fibrosis as precursor lesion of cirrhosis. JAMA 1985; 254:627–630.
22. Marks IN, Bank S, Louw JH, Mashal MG. The clinical varieties of alcoholic pancreatitis in the South Western Cape: A review of 206 cases. S Afr Med J 1965; 39:1093–1097.
23. Durbek JP, Sarles H. Multicenter survey of the etiology of pancreatic diseases. Relationship between the relative risk of developing chronic pancreatitis and alcohol protein and lipid consumption. Digestion 1978; 18:337–350.
24. Reber HA. Alcoholic pancreatitis. In: Howard JM, Jordan GL, Reber Ha, eds. Surgical diseases of the pancreas. 2nd ed. Philadelphia: Lea & Febiger, 1987:284–296.
25. Mendenhall CL, Seef L, Diehl AM, et al. Antibodies to hepatitis B virus and hepatitis C virus in alcoholic hepatitis and cirrhosis: Their prevalence and clinical relevance. Hepatology 1991; 14:581–589.
26. Verbaan H, Andersson K, Eriksson S. Intravenous drug abuse: the major route of hepatitis C virus transmission among alcohol-dependent indivudals? Scand J Gastroenterol 1993; 28:714–718.
27. Orrego H, Blendis LM, Blake JE, Kapur BM. Reliability of assessment of alcohol intake based on personal interviews in a liver clinic. Lancet 1979; 2:1354–1356.
28. Neves MM, Borges DR, Vilela MP. Exocrine pancreatic hypersecretion in Brazilian alcoholics. Am J Gastroenterol 1983; 78:513–516.

Steroid Cell Tumor of the Ovary as a Rare Cause of Virilization

HALIL AZIZLERLI, M.D., REFIK TANAKOL, M.D., TARIK TERZIOĞLU, M.D., FARUK ALAGÖL, M.D., AND FERHUNDE DIZDAROGLU, M.D.

Abstract

Background: Virilization is associated with either ovarian causes, including polycystic ovary syndrome, hyperthecosis, and ovarian tumor, or with adrenal causes, including tumors and congenital adrenal hyperplasia. In establishing the diagnosis, levels of dehydroepiandresterone sulfate, testosterone, and 17α-hydroxyprogesterone (17-OHP), with their response to dexamethasone treatment, should be assessed; and, where indicated, computerized tomography, ultrasound, and selective venous catheterization should be undertaken.

Case Report and Results: A 21-year-old woman presented with a 17-year history of early accelerated linear growth and virilization. During this time, a putative diagnosis of nonclassic congenital adrenal hyperplasia had been made, and she had been treated with glucocorticoids, with no regression in virilization, for 8 years. On presentation to our group, the failure of low- and high-dose dexamethasone suppression tests to decrease blood levels of testosterone and 17-OHP, combined with a relatively low blood level of corticotropin, led us to investigate an androgen-secreting tumor of ovarian origin. When ultrasonography and computerized tomography of the ovaries and adrenal glands displayed no abnormality, selective venous catheterization was performed, revealing an abnormal ovarian-peripheral gradient for testosterone, 17-OHP, estradiol, and androstenedione in the right ovarian vein. On exploratory laparotomy, a neoplasm adjacent to the right ovary was resected and was found to be a steroid cell tumor of the ovary not otherwise specified, one of the rarest tumors causing virilization in children. Symptomatic resolution followed tumor removal.

Conclusion: Selective ovarian and adrenal venous catheterization for hormone assays is an efficient method of identification and localization of an androgen source in virilizing syndromes when noninvasive methods fail.

VIRILIZATION IN PREPUBERTAL GIRLS results from increased circulating androgen levels, usually caused by excessive production by the adrenal glands or ovaries. Adrenal causes of increased production include adrenal neoplasms, congenital adrenal hyperplasia, and Cushing's syndrome. The most common cause of virilization in prepubertal girls is congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency, in which plasma levels of 17α-hydroxyprogesterone (17-OHP) increase. In girls, such defects are frequently recognized at birth because of ambiguous external genitalia. In late-onset forms of CAH ("acquired," "delayed onset," or attenuated), abnormalities may become apparent only after puberty, when hirsutism and amenorrhea become manifest (1). Ovarian causes of hyperandrogenism include polycystic ovaries, hyperthecosis, and several ovarian tumors. When virilization occurs with a peripheral testosterone level exceeding 2 ng/mL, neoplastic hyperandrogenism must

---

From Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology, Metabolism and Nutrition (HA, RT, FA), Istanbul Faculty of Medicine, Division of Endocrine Surgery (TT), and Istanbul Faculty of Medicine, Department of Pathology (FD).

Address reprint requests to Dr. Halil Azizlerli, Professor of Endocrinology and Metabolism, Sakarya Apt. No:8 D:7 Büyükdere caddesi, Şişli, Istanbul, Turkey.

be ruled out (2–4); levels of testosterone between 1.5 and 2 ng/mL should be considered highly suspicious. Preoperative localizing procedures are often valuable and include pelvic ultrasonography, angiography, computerized tomography, magnetic resonance imaging, adrenal scintigraphy with ^{131}iodine-norcholesterol (NP 59 scan), and selective venous catheterization (2, 5–8).

We present a case of prepubertal virilization which had been misdiagnosed as congenital adrenal hyperplasia and was treated with suppressive doses of corticosteroids for 8 years. The patient's actual diagnosis was a steroid cell tumor of the ovary secreting testosterone, 17-OHP, androstenedione, and estradiol (E_2).

Case Report

A 21-year-old woman was referred for primary amenorrhea and virilism. Her parents did not notice any abnormality of her external genitalia at birth. There was no premorbid history of ingestion of medications or drugs and no family history of hirsutism. She was healthy until age 4 years when her parents noticed rapid linear growth.

At age 8 years, she was referred to an endocrinologist because of hirsutism. Her height at that time was 144 cm (far above 95th percentile) and her weight was 31 kg (75th percentile). Her weight by height for that age was at the 5th percentile. (The ideal weight for height was 37.6 kg.) Her plasma level of testosterone was 11.3 ng/mL (39.1 nmol/L), and the 17-OHP level was higher than 20 ng/mL (60.5 nmol/L). Urinary pregnanetriol excretion was greater than 14 mg every 24 hours (59.44 μmol/24 h) and urinary 17-ketosteroid levels were elevated to 50 mg/day (173.35 μmol/day). A peripheral blood chromosome study revealed a normal 46XX pattern. Her physician prescribed cortisone therapy at a dose of 0.65 mg/kg per day (20 mg/day) with the presumed diagnosis of congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency. According to her parents, virilism progressed under this treatment and her linear growth ceased at the age of 10 years, at which time she was the tallest among her peers.

In 1979, she was examined at an endocrine clinic. Despite the lack of a detailed medical report, available laboratory reports indicated that no suppression of testosterone and 17-OHP was detected after administration of 2 mg or 8 mg of dexamethasone. That same year, cortisone was replaced by hydrocortisone at a dose of 25 mg/day in another clinic. Although she was advised to have regular follow-up every 3 months, she did not see a physician for the next 8 years; during this period, she stated that she took hydrocortisone, 25 mg/day, continuously without any relief. Then she stopped taking the drug for the next 4 years. During this time, she noted a gradual increase in facial and body hair. She had never menstruated, and no mammary development had occurred.

On January 11, 1990, the patient presented to the endocrine clinic at Istanbul Faculty of Medicine for the first time. Physical examination revealed a slim, muscular female in no acute distress. She was 147 cm tall (far below the 5th percentile), had a masculine habitus, and weighed 50 kg (15th percentile). Her weight for height for that age was at the 25th percentile. (The ideal weight for height was 56.9 kg.) Her blood pressure was 110/80 mm Hg, her pulse rate was 80 beats per minute, and the remainder of her vital signs were unremarkable. Her voice was deep and husky. No mammary development was noted. A full male-type shaven beard was present. Coarse black hair covered the chest, upper and lower arms, shoulders, back, abdomen, and legs. She had marked central and frontotemporal balding. No Cushingoid features were noted. The heart and lungs were unremarkable. No abdominal or pelvic masses were palpable. Galactorrhea was not present. The external genitalia and pelvic examination were normal except for an enlarged clitoris which was 1.5 cm in length and 0.6 cm in diameter. The hymen was intact. The remainder of the physical examination was normal, including the neurologic evaluation. Laboratory values were significant for a hematocrit of 0.464, erythrocyte sedimentation rate of 6 mm/hour, fasting blood glucose of 61 mg/dL (3.4 mmol/L), and serum electrolytes within normal limits. Plasma levels of luteinizing and follicle-stimulating hormones were 1.5 and 0.7 IU/L, respectively; and the serum prolactin level was 12.6 μg/L. Corticotropin levels ranged from 4.1 to 6.1 pg/mL. Urinary excretion of 17-ketosteroids was 58 mg/day (201 μmol/day). Serum levels of steroids were measured before and after 2-mg and 8-mg dexamethasone suppression tests (**Table 1**). Ultrasonography of the ovaries and adrenal glands revealed no abnormality, but the right ovary was not well visualized. Computerized axial tomography of the abdomen and pelvis revealed normal adrenal glands, but the ovaries were not clearly visualized. Computed tomography scan of the head and sella demonstrated no abnormality. Retrograde femoral vein catheterization and se-

TABLE 1

Peripheral and Ovarian Venous Concentrations of Various Steroids during Preoperative and Postoperative Evaluation

	E_2	A_2	DHEA-S	17-OHP	T	F
Peripheral vein	1147	11.7	2063	85	5.2	10
2 mg DXM supp	—	—	2173	80	6.3	2.3
8 mg DXM supp	—	—	—	85	6.9	2.6
Right ovarian	12,800	1450	3205	2200	160	11.8
Left ovarian	666	35	3205	90	5.5	10.6
OPG	11,653	1438	1142	2115	154.8	1.8
Upper-normal OPG (ref. 6)	1100	35.3	—	12.3	0.59	—
Postoperative	13.9	0.58	—	0.09	0.09	—

E_2, estradiol (pg/mL) (SI units = C [conventional units] × 3.67); A_2, androstenedione (ng/mL) (SI = C × 3.492); DHEA-S, dehydroepiandrosterone sulfate (μg/L) (SI = C × 0.002714); 17-OHP, 17 α-hydroxyprogesterone (ng/mL) (SI = C × 3.026); T, testosterone (ng/mL) (SI = C × 3.467); F, cortisol (μg/dL) (SI = C × 27.59); DXM supp, dexamethasone supp; OPG, ovarian-peripheral vein gradient (calculated as in Reference 6).

lective venous sampling displayed a marked step-up of steroids in the right ovarian vein (Table 1).

The patient underwent exploratory laparotomy on May 12, 1990. A yellow-brown tumor arising from the hilar aspect of the right ovary was found and removed. The patient had an uneventful postoperative course. After removal of the tumor, the serum levels of steroids fell rapidly (Table 1). Within 6 months, the patient began menstruating regularly and mammary development reached Tanner grade 3. She noted considerable diminution in facial and body hair. The patient did not regain a completely normal feminine voice, but noticed hair growth over the bald area. All other previously noted physical signs of virilization have since disappeared, except no significant decrease in the size of the clitoris has occurred.

Pathologic Findings

The tumor was moderately firm and weighed 53.8 g; it measured 6 cm × 3.5 cm × 1.5 cm in size. Macroscopically, the lesion was yellow; and, on cross-section, it was brown (**Fig. 1**).

The paraffin-embedded hematoxylin and eosin-stained sections of the tumor revealed large, polygonal cells with round, regular nuclei and a finely granular cytoplasm, consistent with steroid cell tumor of the ovary (**Fig. 2**). On some sections, the presence of fibrofatty tissue was suggestive of an origin in adrenal cortical nests. Reinke's crystalloids were not found.

On electron microscopy, a nearly homogeneous population of large cells, each of which had a large, round, granular nucleus and a single, prominent nucleolus, was seen (**Fig. 3**). The cytoplasm, at higher magnification, contained many small, oval mitochondria, many lipid-containing, electron dense granules, a significant number of Golgi complexes, and numerous lamellar inclusions that appeared to be contracted, concentric, smooth endoplasmic reticulum. On the surface of the cells, small microvilli were observed. Some cells had small desmosomes. Small patches of basement membrane were present; and, in many instances, these appeared adjacent to the microvilli. There was no evidence of Reinke's crystalloids. The ultrastructure of this mass was consistent with a steroid-secreting cell.

Discussion

In the case presented, nonclassic or late-onset 21-hydroxylase deficiency was the presumed diagnosis, although low- and high-dose dexamethasone suppression tests and long-term corticosteroid treatment all failed to inhibit high levels of testosterone and 17-OHP. These findings, and the results of selective venous sampling, were consistent with the presence of an androgen-secreting

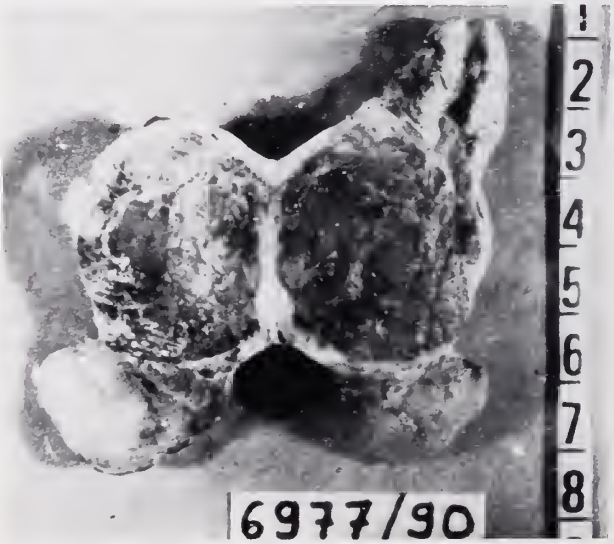


Fig. 1. Cross-section of the ovary. The tumor is demarcated from the adjacent ovary by its dark brown color.

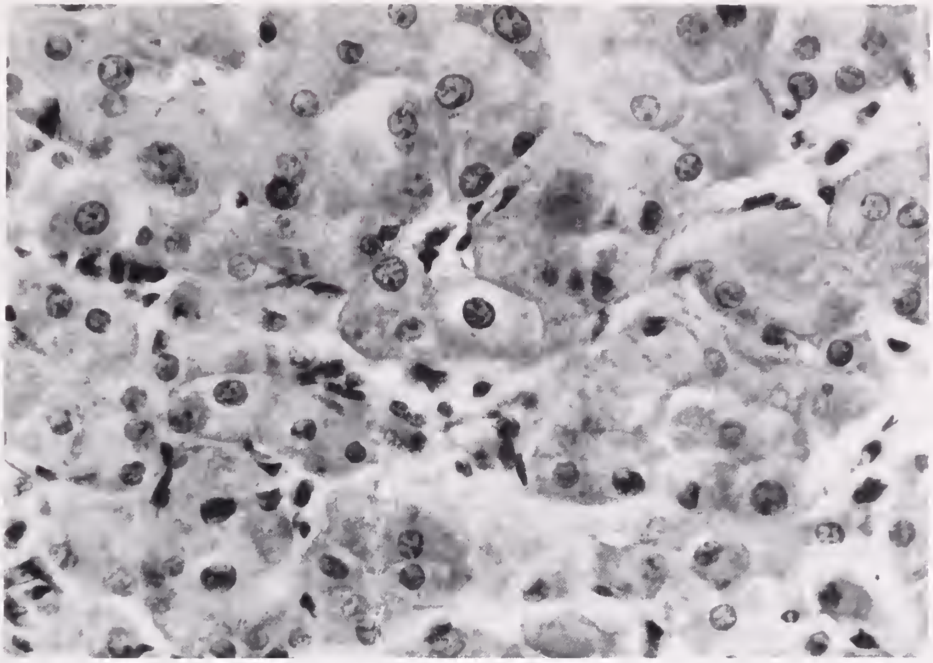


Fig. 2. Microscopic appearance of the ovarian tumor. The tumor is composed of large polygonal cells with round, regular nuclei. The cytoplasms of the cells are finely granular and acidophilic (hematoxylin and eosin, ×310).

neoplasm; a steroid cell tumor of the ovary was found on laparotomy.

Ovarian steroid cell tumors, which may secrete various steroids, are among the uncommon causes of virilization (5, 6). In the past, many names have been applied to ovarian steroid cell tumors, i.e., lipoid cell tumor, lipid cell tumor, adrenal-like tumor, masculinovoblastoma, luteoma, hypernephroid tumor, and adrenal rest tumor, demonstrating the difficulty in determining the cellular lineage of the neoplasm and its precise categorization (5–8).

Steroid cell tumors comprise steroid hormone-producing cells, resembling lutein cells, Leydig cells, and adrenal cortical cells morphologically. Steroid cell tumors of the ovary can be

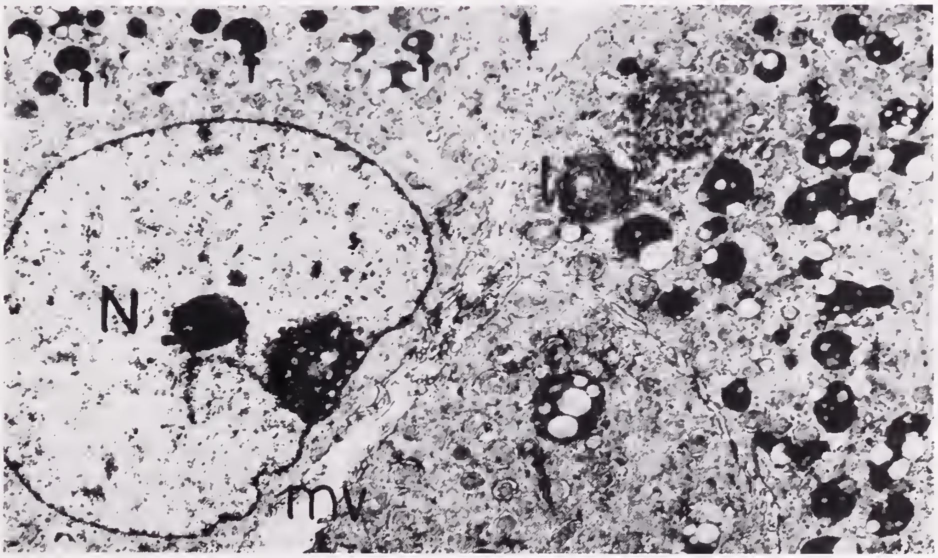


Fig. 3. Ultrasturctural appearance of the lipid cell tumor of the ovary. The cytoplasms of the tumor cells contain many lipid-containing electron dense granules (arrows); and some lamellar inclusions (Li); N is the nucleus. On the surface of the cells, small microvilli (mv) are seen. (Fixed with 1% osmium tetroxide and stained with uranyl acetate-lead sitrate, ×10 000. Electron microscopy was performed using a Zeiss 9S-2, JEOL 100C electron microscope.)

conveniently divided into three subgroups: stromal luteoma, Leydig cell tumor, and steroid cell tumor not otherwise specified (NOS).

Stromal luteoma may be diagnosed in the presence of a small neoplasm composed of luteinized stromal cells within the ovarian stroma (especially when associated with hyperthecosis ovarii).

In the Leydig cell tumor (Hilus cell tumor), the cytoplasms of the steroid-secreting cells contain Reinke's crystalloids, composed of protein-containing, tightly apposed, 300-Å-wide, hexagonal, microtubular units (2, 5, 7, 8). A subclassification of Leydig cell tumors has been called "probable hilus cell tumors," which remain in the NOS category of steroid cell tumors (5, 7–9). These tumors have the same histologic characteristics as Leydig cell tumors but lack Reinke's crystalloids (5, 7, 8).

Two thirds of the steroid cell tumors cannot be considered classified as either stromal luteoma or Leydig cell tumor. These are considered NOS. This classification seems more appropriate than the designation "lipid" or "lipoid" cell tumor used in the past because of lack of specificity of these terms and the paucity or absence of fat in approximately one fourth of the tumors in this category (5, 7, 9).

The tumor in the case presented has histologic characteristics in common with steroid cell tumor NOS. Steroid cell tumors NOS have been reported to secrete not only androstenedione (its main secretion) (5, 10, 11), but also progesterone, 17-OHP, dehydroepiandrosterone sulfate (DHEA-S), 17-hydroxypregnenolone, and E_2 (3, 10, 12). In fact, the secretion rate of 17-OHP is much higher than any other steroid secreted by the tumor in some steroid cell tumors (2–4, 7, 11, 13). *In vivo* studies of tumor products may be accomplished by calculating the ovarian-peripheral gradient of each steroid and comparing it with the upper limit of healthy women (2, 5, 6). Based on the dominant ratio method (14), the major products of our patient's tumor were testosterone, 17-OHP, androstenedione, and E_2 (Table 1). Although DHEA-S was not elevated in this case, the increase in urinary 17-ketosteroid levels can be explained by the secretion of androstenedione by the tumor.

Most steroid cell tumors NOS occur during the reproductive and middle-age years, with an average age of 43 years (2). Ten to thirty years may pass between onset of symptoms and diagnosis (5). One may presume that the tumor was present in our patient since she was 4 years of age and was probably the cause of her rapid growth in early childhood and later virilization. The interval between the onset of her symptoms and the definitive diagnosis was 17 years.

In an extensive review of the world literature on primary ovarian tumors and steroid cell tumors in patients younger than 20 years, Harris et al. (7) noted that steroid cell tumors were previously reported only in a total of 22 prepubertal children, including their own patient. All of those patients, ranging in age from 2½ years to 13½ years, presented with virilization except one with Cushing's syndrome and another with isosexual pseudoprecocity. Of the 22 cases, 10 patients had hilus cell tumor and 3 patients had definite steroid cells tumor NOS. Because the remaining nine cases did not have a detailed histologic description, they could retrospectively be designed lipoid cell tumor or adrenal rest tumor (more appropriately steroid cell tumor), without any further subgrouping. The patient reported by Harris et al. (7) was an 8-year-old girl with a clinical course similar to our patient's. She was treated with cortisone acetate, with the presumed diagnosis of late-onset 21-hydroxylase deficiency, without any relief; subsequently, a steroid cell tumor NOS, 3.5 cm in diameter, was found in the left ovary (7). In another case report, a six-year-old girl, with adrenogenital syndrome, underwent unilateral adrenalectomy before a steroid cell tumor NOS was found in the ovary at the age of 8 years (15).

The preoperative diagnosis and localization of steroid-secreting tumors are of utmost clinical importance, because the localization of these tumors sometimes may not be possible even at laparotomy (2). Negative results on ultrasonography and computerized tomography, as in our case, do not exclude the presence of neoplastic hyperandrogenism because, as has been reported previously, ovarian tumors measuring up to 3 cm have been missed by imaging procedure (2, 3, 11, 16). Moltz et al. (4) reported that in six of their seven patients with histologically proven gonadal neoplasms, diagnostic methods such as laparoscopy, radiography, retrograde venography, iodocholesterol scanning, and even laparotomy failed to locate occult, virilizing, gonadal neoplasms with diameters between 0.6 and 2.2 cm; ovarian and adrenal vein catheterization facilitated the localization of the tumor in five of these patients.

Selective venous catheterization is superior to other diagnostic procedures because it detects functional secretory activity of the tumor, regardless of its size. In our case, the value of selective venous catheterization is again proven as a precise method of identifying the hypersecretory source of androgens in patients with virilizing ovarian tumors.

Acknowledgments

The authors are grateful to Professor L. Deligdisch and Dr. R. Gordon from the Mount Sinai Medical Center for their review of the histologic sections and electron microscopic study. We would like to thank Ömer Güzel, Biruni Laboratories, for his kind support in laboratory investigations and to Asim Berzeg, radiologist of the American Hospital in Istanbul, for performing selective vein catheherization. We also thank Ms. Sylvia Seden for her help in preparing the manuscript.

References

1. Kohn B, Levine LS, Pollack M, et al. Late-onset steroid 21-hydroxylase deficiency: A variant of classical congenital adrenal hyperplasia. J Clin Endrocinol Metab 1982; 55:817–827.
2. Nagamani M, Gonzales-Vitale JC. Steroid secretion patterns of a hilus cell tumor of the ovary. Obstet Gynecol 1981; 58:521–527.
3. Adashi EY, Rosenwaks Z, Lee PA, Seegar G, Migeon CJ. Endocrine features of an adrenal like tumor of the ovary. J Clin Endocrinol Metab 1979; 48:241–245.
4. Moltz L, Pickartz H, Sorensen R, Schwartz U, Hammerstein J. Ovarian and adrenal vein steroids in seven patients with androgen-secreting ovarian neoplasms: Selective catheterization findings. Fertil Steril 1984; 42: 585–593.
5. Barkan AL, Cassorla F, Loriaux DY, Kelch RP, Marshall JC. Steroid and gonadotropin secretion in a patient with a 30-year history of virilization due to lipoid cell ovarian tumor. Obstet Gynecol 1984; 64:287–295.
6. Meldrum DR, Abraham GE. Peripheral and ovarian venous concentrations of various steroid hormones in virilizing ovarian tumors. Obstet Gynecol 1979; 53:36–43.
7. Harris CA, Wakely PE, Kaplowitz PB, Lowinger RD. Steroid cell tumor of the ovary in a child. Arch Pathol Lab Med 1991; 115:150–154.
8. Davidson BJ, Waisman J, Judd HL. Long standing virilism in a woman with hyperplasia and neoplasia of ovarian lipidic cells. Obstet Gynecol 1981; 58:753–759.
9. Paraskeras M, Scully RE. Hilus cell tumor of the ovary: A clinicopathological analysis of 12 Reinke crystal positive and nine crystal negative cases. Int J Gynecol Pathol 1989; 8:299–310.
10. Bonaventrua LM, Judd H, Roth LM, Cleary RE. Androgen, estrogen and progestogen production by a lipid cell tumor of the ovary. Am J Obstet Grynecol 1978; 131: 403–409.
11. Imperato-McGinley J, Peterson RE, Dawood MY, et al. Steroid hormone secretion from a virilizing lipoid cell tumor of the ovary. Obstet Gynecol 1981; 57:525–531.
12. Lipsett MB, Kirschner MA, Wilson H, Bardin W. Malignant lipid cell tumor of the ovary: Clinical, biochemical and etiologic considerations. J Clin Endocrinol 1970; 30:336–344.
13. Morrow LB, Thompson RJ, Mellinger RC. Ovarian lipoid cell tumor: Urinary steroid response to adrenocorticotropin and chorionic gonadotropin. J Clin Endocrinol 1968; 28:1756–1762.
14. Mandel FP, Voet RL, Weiland AJ, Judd HL. Steroid secretion by masculinizing and feminizing hilus cell tumors. J Clin Endocrinol Metab 1981; 52:779–784.
15. Motlik K, Starka L. Adrenocortical tumor of the ovary. A case report with particular stress upon morphological and biochemical findings. Neoplasm 1973; 20:97–110.
16. Aleem FA, Spenillo AR, Oberlander S, Surks MI. Hilar cell tumor of the ovary: Preoperative localization by selective retrograde venous sampling. Obstet Gynecol 1980; 56:99–102.

Seminar

Arrhythmias and Antiarrhythmic Drugs

BRIAN F. HOFFMAN, M.D.

DESPITE STUDIES OVER MANY YEARS on the electrophysiological mechanisms for arrhythmias and parallel studies on the mechanisms of action of antiarrhythmic drugs, the pharmacological treatment of most arrhythmias is far from satisfactory. It is reasonable to ask why the multitude of drugs that have resulted from these studies has not provided the desired efficacy in the absence of arrhythmogenicity. There is no single answer to this question, but there are several partial answers that may lead to future advances in the art.

One contributing factor is the fact that the development, as well as the use, of antiarrhythmic drugs proceeded without serious concern for the probable electrophysiological mechanisms for the arrhythmias being treated. For many years a drug was selected on the basis of prior experience in treating apparently similar arrhythmias and a simplistic model of arrhythmogenic mechanisms. Drug development concentrated on identifying agents that resembled known drugs in terms of primary actions and differed in terms of subsidiary actions or pharmacokinetic properties.

Early studies recognized two general mechanisms for arrhythmias: reentry and focal excitation. Reentrant excitation could be demonstrated in isolated tissues (1,2) and the *in situ* heart (3) and it was clear that during reentry there must be an excitable gap in the reentrant circuit between receding refractoriness and the oncoming impulse. It was postulated that an agent that prolonged refractoriness more than it slowed conduction would tend to abolish the excitable gap and terminate reentry, whereas one that slowed conduction more than it prolonged refractoriness would tend to sustain reentry (4). Quinidine, the first widely used antiarrhythmic drug, exerted both actions and was not uniformly effective for either supraventricular or ventricular reentrant rhythms. Because there was little experimental evidence concerning the electrophysiological mechanism for spontaneous impulse generation, studies on arrhythmias from focal excitation were more limited. These emphasized the creation of an artificial site of impulse origin by focal application of excitants such as aconitine (5) or the use of electric current. Drugs were classified in terms of their major actions (Table 1) even though it was recognized that selectivity or specificity in most instances was quite limited.

Models of the basis for reentrant excitation included a segment of the reentrant circuit in which there was slow conduction and a tendency for unidirectional block of a premature impulse. These models permitted an understanding of the initiation of reentrant excitation and the responses of a reentrant rhythm to premature stimulation and overdrive (6,7). Also, they provided an explanation of the termination of reentry by local anesthetic antiarrhythmics like quinidine, procainamide, and lidocaine. It was reasonable to assume that, in the segment demonstrating slow conduction, the impulse-generating capability of the fibers was reduced. Thus the ability of the drugs to depress excitability and responsiveness would result in bidirectional conduction block in the depressed segment at a concentration causing only modest or no slowing of conduction in the remainder of the heart. In terms of this type of model it was possible to consider drugs that depressed conduction without prolonging refractoriness as suitable treatment for reentrant rhythms. One group of drugs, including lidocaine, tocainide, and mexiletine, shortened refractoriness and had virtually no effect on conduction in normal fibers but significantly depressed conduction in partially depolarized fibers. A second group, including flecainide and propafenone, markedly slowed conduction in all fibers but failed consistently to modify refractoriness. Both types were effective for some reentrant arrhythmias but in-

---

Adapted from a seminar at Mount Sinai School of Medicine, Department of Pharmacology.

From the Department of Pharmacology, College of Physicians & Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032.

TABLE 1
Antiarrhythmic Drug Classification

	Class	Examples
I.	Sodium channel block	
	A. Slow conduction, usually delay repolarization	Quinidine, procainamide, disopyramide, moricizine
	B. Minimal effect on conduction,[a] usually accelerate repolarization	Lidocaine, mexiletine, tocainide, phenytoin
	C. Markedly slow conduction, usually little effect on repolarization	Flecainide, propafenone, indecanide
II.	β-Adrenergic block	
	No effect on conduction, variable effect on repolarization	Propranolol, acebutolol, esmolol, others
III.	Potassium channel block	
	No effect on conduction, delay repolarization	Bretylium, sotalol, amiodarone
IV.	Calcium channel block	
	Impair conduction in model tissues, variable effects on repolarization	Verapamil, diltiazem

Modified from Vaughan-Williams and Harrison (21,22).
[a] Conduction depressed in abnormal fibers.

effective for many, even though the mechanism seemed to be the same.

Parenthetically, it is interesting to ask if the lack of prolongation of refractoriness demonstrated in the usual type of pharmacological studies is true for the effect of the drug during a reentrant rhythm. The postulate is that the local anesthetic antiarrhythmic drug will slow and finally block conduction in the slowly conducting segment of the reentrant circuit. If the local slowing of conduction is marked, the action potential just proximal to this area of slowing will be prolonged significantly (8,9). This results from electrotonic interaction between the slowly propagating impulse and the not-yet repolarized fibers behind it. It thus is possible that block of the reentrant impulse by the local anesthetic antiarrhythmic drug actually results from delay of repolarization and an effect on the duration of the excitable gap at a crucial site in the circuit.

Electrophysiological Mechanisms for Arrhythmias

Data obtained from studies on the transmembrane potentials of cardiac fibers and on the electrophysiology of the heart suggested that it was possible to categorize the general mechanisms for arrhythmias in terms of identified electrophysiological mechanisms (Table 2) (10,11). This classification proposed that arrhythmias resulted from disorders either of impulse origin or conduction or simultaneous abnormalities of both. Abnormalities of impulse origin might result from automatic activity or triggering: the generation of an additional action potential by a preceding one. For automatic rhythms two mechanisms were postulated: normal and abnormal automaticity. For triggered arrhythmias there were also two classes: impulses generated by early or delayed afterdepolarizations. Disturbances of rhythm caused by abnormal conduction included two major subdivisions: failure of impulse conduction, as in sinoatrial or atrioventricular block, and reentrant excitation. Reentry was further subdivided in terms of the stability of the reentrant path. Somewhat later the mechanisms for reentrant excitation were modified to include reflection (12,13). In this case the propagation of the impulse slows markedly and gives rise to a new wave of excitation that propagates back over the same path used by the slowly propagating impulse.

It was recognized that, when a reentrant path included an area of slow conduction and unidirectional block, the propagating impulse might be a depressed fast response in which the action potential upstroke results from inward sodium current, or a slow response in which the L-type calcium current generates the upstroke (14). Slow responses clearly were participants in atrioventricular nodal or sinus nodal reentry but also were implicated in reentrant circuits in which partial depolarization had inactivated the sodium channels. This partial list of possible mechanisms for arrhythmias strongly suggests that there are multiple possible targets for antiarrhythmic

TABLE 2
Electrophysiological Mechanisms for Cardiac Arrhythmias

- Abnormal impulse initiation
  - Automaticity
    - Normal automaticity
    - Abnormal automaticity
  - Triggered activity
    - Early afterdepolarizations
    - Delayed afterdepolarizations
- Abnormal impulse conduction
  - Conduction block leading to ectopic pacemaker “escape”
  - Unidirectional block and reentry
    - Ordered reentry
    - Random reentry
  - Reflection
- Simultaneous abnormalities of impulse generation and conduction
  - Impaired conduction caused by Phase 4 depolarization
  - Parasystole

agents and that a rational approach to both treatment as well as drug development could be based on this concept.

The Gambit Approach

The first systemic consideration of the possibility of selecting an antiarrhythmic drug in terms of the electrophysiological mechanisms for the arrhythmias, as well as in terms of prior experience, was presented in a paper entitled "The Sicilian Gambit: A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms" (15). The essence of the Gambit scheme was first to identify as precisely as possible the mechanism and then, in terms of this mechanism, find the vulnerable parameter (Table 3). This parameter was the physiological function that, if modified in an appropriate manner, was most likely to inactivate the arrhythmogenic mechanism without causing adverse cardiac electrophysiological effects. The general approach had several advantages. First, it provided a logical basis for drug selection; second, it indirectly identified mechanisms and vulnerable parameters for which suitable drugs were not available. Several examples can be considered.

Early afterdepolarizations (EAD) are the cause of torsades-like arrhythmias. Frequently these EAD result from administration of antiarrhythmic drugs, as with quinidine or dofetilide. In general, EAD occur when repolarization is excessively delayed. The delay in repolarization may result either from a diminished outward current during the action potential plateau or from an excess inward current. The former would result from a decrease in outward potassium current carried by the delayed rectifier channels and the latter from a prolongation of inward sodium current caused by delayed inactivation of the sodium channels. An illustrative example of this is provided by the congenital prolonged Q-T syndrome. Recent studies have shown that, in such patients, the prolonged repolarization and DAD-induced arrhythmias may be caused by a genetic abnormality of the sodium channel or a genetic abnormality of the delayed rectifier potassium channel I_{Kr}. In the former case, LQT-3, the change in sodium channel function delays inactivation and permits a small, persistent increment in inward current during the plateau. This abnormal inward current obviously is the vulnerable parameter. It has been demonstrated that local anesthetic arrhythmics such as lidocaine will block the abnormal current at concentrations in-

TABLE 3

Classification of Arrhythmogenic Mechanisms at the Cellular Level in Terms of Vulnerable Parameters

Mechanisms of arrhythmia	Vulnerable parameter (antiarrhythmic effect)	Ionic currents most likely to modulate vulnerable parameter
Automaticity		
Enhanced normal automaticity	Phase 4 depolarization (decreased)	I_f ; $I_{Ca\text{-}T}$ (block) $I_{K(ACh)}$ (activate)
Abnormal automaticity	Maximum diastolic potential (hyperpolarize) or	I_K ; $I_{K(ACh)}$ (activate)
	Phase 4 depolarization (decrease)	$I_{Ca\text{-}L}$; L_{Na} (block)
Triggered activity based on		
Early afterdepolarizations	Action potential duration (shorten) or	I_K (activate)
	early afterdepolarizations (suppress)	$I_{Ca\text{-}L}$; I_{Na} (block)
Delayed afterdepolarizations	Calcium overload (unload) or delayed	$I_{Ca\text{-}L}$ (block)
	afterdepolarizations (suppress)	$I_{Ca\text{-}L}$; I_{Na} (block)
Reentry		
Primary impaired conduction (long excitable gap) caused by depressed Na^+ channels	Decrease excitability and conduction	I_{Na} (block)
Primary impaired conduction (long excitable gap) caused by slow calcium current	Decrease excitability and conduction	$I_{Ca\text{-}L}$ (block)
Primary impaired conduction (long excitable gap) caused by anisotropy	Decrease excitability and conduction	Gap junction (block)
Conduction encroaching on refractoriness (short excitable gap)	Effective refractory period (prolong)	I_K (block) (I_{Na} ; $I_{Ca\text{-}L}$ (increase)

Modified from Members of the Sicilian Gambit. Antiarrhythmic Therapy: a Pathophysiologic Approach. Armonk, NY: Futura Publishing Co., 1994.

sufficient to modify the action potential upstroke or slow propagation (16).

Studies in patients have shown that mexiletine, a lidocaine analog, is effective in preventing arrhythmias and restoring the Q-T interval to normal in patients with this congenital abnormality (17). This provides a good example of the reasonableness of the Gambit approach. Delayed repolarization is caused by a prolongation of sodium current. The sodium channel thus is the vulnerable parameter. A drug providing suitable block of this channel is effective and safe.

However, the concepts embodied in the Gambit approach to selection of antiarrhythmic agents, although sound, probably is incomplete. It is incomplete because it largely ignores the innate complexity of the electrophysiological basis for electrical activity in any type of cardiac tissue and the important regional differences between nodes, atria, ventricles, and conducting system. Compounding this is the fact that disease leading to arrhythmia generation can and often does modify the electrophysiological properties of the cardiac fibers responsible for the arrhythmia (18). Such modifications, about which we know very little, obviously can change the response to an antiarrhythmic drug, either decreasing efficacy or enhancing arrhythmogenicity.

Ionic Currents Underlying Electrical Activity

A typical ventricular muscle fiber is the usual model for descriptions of the basis for cardiac electrical activity. When quiescent such a fiber maintains a steady resting potential so that the inside of the fiber is 85 to 90 mV negative with respect to the outside. The resting potential results from the potassium concentration gradient across the membrane and the fact that, at -90 mV, the membrane is predominantly permeable to potassium. The channel conferring this permeability is the inward rectifier, I_{K1}. If a stimulus decreases the transmembrane potential sufficiently, a different current, sodium, sets the transmembrane potential. The sodium channel, I_{Na}, senses the transmembrane voltage gradient. On depolarization the sodium channels change from a closed to an open state and permit an intense inward current that causes the action potential upstroke. Generally, after opening, most of the sodium channels promptly inactivate and cease to conduct. Recovery from inactivation requires repolarization. It is worthwhile to note that the affinity of antiarrhythmic drugs for the sodium channel typically differs for the resting or closed, the open and the inactivated states as does dissociation of drug from the channel.

Inactivation of sodium channels terminates the action potential upstroke; the subsequent voltage-time course of the transmembrane potential depends on sequential contributions from several currents. The first of these, responsible for Phase 1 of repolarization, is the transient outward current I_{to1}. I_{to1}, like the sodium channel, is voltage-gated: it opens on depolarization, inactivates, and requires repolarization to remove inactivation. This current is most prominent in fibers of the midwall of the ventricle, the so-called M cells (19), less prominent in subendocardial fibers and of minimal importance in subepicardial fibers. This regional difference in current density is partly responsible for the transmural gradient of action potential duration.

I_{to1} is a strong determinant of action potential duration because it modifies the magnitude and time course of the subsequent calcium current, I_{CaL}. The channels that carry the L-type calcium current also are voltage-gated, opening on depolarization. The speed with which this current develops, as well as its magnitude and duration, vary as a function of the extent of repolarization during Phase 1. With minimal repolarization the calcium channels open rapidly and the peak current is high; with greater repolarization during Phase 1 the calcium current develops less rapidly, its peak value is reduced but it persists for a longer time. The action potential is prolonged proportionately.

The interdependence among the several channels is even more complex than this. The inward calcium current initiates contraction by increasing $[Ca^{2+}]_i$. However, this increase in $[Ca^{2+}]_i$ also influences membrane ionic currents. It contributes to inactivation of the L-type calcium channels but activates an additional transient outward current channel which is predominantly permeable to chloride.

What does this imply in relation to predictable effects of an antiarrhythmic drug? Quinidine, the oldest member of Class I, blocks sodium channels. However, it also blocks I_{to1} and thus will influence the complex interactions described above. This influence will be stronger in areas in which I_{to1} is prominent, as in M cells, than in epicardium in which it is weak. Also, it has been shown that in ventricular myocardial cells that survive infarction I_{to1} is markedly attenuated or abolished (20); in such fibers the effects of quinidine also must be modified.

The L-type calcium current is primarily responsible for maintaining the plateau of the action potential. Repolarization occurs because I_{CaL} inactivates and delayed rectifier currents are activated. The delayed rectifier currents are outward potassium currents and, in ventricle, two are best known and probably most important. One is called I_{Kr} because it activates rapidly and the other, I_{Ks} because it activates quite slowly. In all likelihood both probably make important contributions to repolarization. I_{Kr} activates at a less positive voltage than does I_{Ks}; the extent to which the latter is activated depends on the transmembrane potential during the plateau and plateau duration. We thus see that the effects of alterations in I_{to1}, described above, can influence the magnitude of one of the delayed rectifier currents and the timing of repolarization. Finally, it is important to recognize that, as the membrane repolarizes during Phase 3, an additional outward current plays a role. This is I_{K1}, the current we have characterized as being primarily responsible for the resting potential. As membrane potential shifts from the plateau value, near 0 mV, in a negative direction, I_{K1} delivers an important surge of repolarizing current that reaches a peak and then, as membrane potential approaches the resting (potassium equilibrium) potential, declines.

In addition to these important currents that act on membrane potential during the plateau and Phase 3 one also must consider other sources of current. The sodium channel largely inactivates at the end of the action potential upstroke but inactivation is not complete. As a result there is some inward current during the plateau. It can be shown that this residual sodium current is sufficient to influence action potential duration. The sodium that enters the fiber during the action potential is extruded by the so-called sodium pump. The pump extrudes 3 Na^+ in exchange for 2 K^+ and thus provides an outward current that has demonstrable effects on both the magnitude of the resting potential and the duration of the plateau. Finally, the calcium ions that enter to trigger contraction also must be extruded and this is accomplished by the Na/Ca exchanger. The exchanger transfers 1 Ca^{2+} in exchange for 3 Na^+ and thus, like the pump, contributes to net membrane current. The direction of the current (inward/outward) depends on the balance between the transmembrane potential and the equilibrium potentials for the two transported ions. Obviously a drug-induced decrease in sodium current will modify the contributions by both the sodium pump and Na/Ca exchanger to membrane potential. Also, any change in calcium current in the L-type calcium channel will have an effect on the current provided by the Na/Ca exchanger.

Conclusions

What does the innate complexity of electrogenesis in heart fiber imply with respect to rational design and selection of antiarrhythmic drugs? Obviously the concept of selectivity has limited applicability. Even though a drug may interact with only one class of membrane ion channels, the effect of modifying current in that channel very often will influence one or more additional currents. It thus may not be a simple matter to predict the net effect of the drug or, for that matter, to attribute its actions to an effect on the specific channel with which it interacts. Admittedly, in patients with the LQT3 abnormality, lidocaine blocks the abnormal inward sodium current at a concentration having little or no effect on the action potential upstroke or conduction, and mexiletine seems to be a specific for the abnormalities demonstrated by the patient. Nevertheless, this selectivity very likely results from the fact that the slowly inactivating channels are inherently more sensitive to the local anesthetic antiarrhythmics than are the sodium channels generating the action potential upstroke. Until more evidence is available, it probably is unrealistic to assume that selection of an antiarrhythmic drug in terms of an identified vulnerable parameter always will provide the desired degree of selectivity.

Another example may be considered that involves patients in whom Q-T prolongation and torsades result from an abnormality of the delayed rectifier channel I_{Kr}, those with LQT2. In such patients the action potential prolongation results from a decrease in repolarizing potassium current. A drug that selectively increases this current is not available. However, because maintenance of the plateau depends on the balance between inward and outward currents, i.e., the net membrane current, one might postulate that a decrease in sodium current, as well as an increase in potassium current, should be able to normalize repolarization. Limited studies (17) have shown that this may not be true. Mexiletine fails to significantly shorten the Q-T interval in most of such patients. At present the reasons for this are unclear.

In summary, it probably is reasonable to base selection of an antiarrhythmic drug on an understanding of the electrophysiological mechanism for the arrhythmia, when this is known, and to direct the drug action against a rationally selected vulnerable parameter. However, at present, this course of action will be of value mainly in helping to identify limits in our understanding of arrhythmogenic mechanisms and drug actions and suggesting different and improved design of new pharmacological agents.

Acknowledgment

Original studies were supported in part by Grant HL-08508 from the National Heart, Lung and Blood Institute, National Institutes of Health.

References

1. Mayer AG. Rhythmical pulsation in scyphomedusae. DC: Carnegie Institution, Washington, 1906.
2. Mines GR. On circulation excitations in heart muscles and their possible relation to tachycardia and fibrillation. Trans R Soc Can 1914; 4:43.
3. Lewis T. Observations upon a curious and not uncommon form of extreme acceleration of the auricle: Auricular flutter. Heart 1913; 4:171.
4. Lewis T. Clinical disorders of the heart beat. New York: Paul B. Hoeher Publisher, 1918.
5. Scherf D, Schaffer AI, Blumenfeld S. Mechanism of flutter and fibrillation. Arch Intern Med 1953; 91:333.
6. Waldecker B, Coromilas J, Saltman AE, Dillon SM, Wit AL. Overdrive stimulation of functional reentrant circuits causing ventricular tachycardia in the infarcted canine heart: Resetting and entrainment. Circulation 1993; 87:1286–1305.
7. Waldo AL, Carlson MD, Biblo LA, Henthorn RW. The transient entrainment concept in understanding atrial flutter. In: P Touboul, AL Waldo, eds. Atrial arrhythmias: Current concepts and management. St. Louis: Mosby Year Book Publishers, 1990:210.
8. Luo CH, Rudy Y. A dynamic model of the cardiac ventricular action potential. Depolarization, repolarization and their interactions. Circ Res 1991; 68:1501–1526.
9. Joyner RW, Kumar R, Wilders R, Jongsma HJ, Verheijck EE, Golod DA, van Ginneken ACG, Wagneer MB, Goolsby WN. Modulating L-type calcium current affects discontinuous cardiac action potential conduction. Biophys J 1996; 71:237–245.
10. Hoffman BF, Cranefield PF. The physiological basis of cardiac arrhythmias. Am J Med 1964; 37:670–684.
11. Hoffman BF, Rosen MR. Cellular mechanisms for cardiac arrhythmias. Circ Res 1981; 49:1–15.
12. Spinelli W, Hoffman BF. Mechanisms of termination of reentrant arrhythmia by class I and class III antiarrhythmic agents. Circ Res 1989; 65:1565–1579.
13. Cranefield PF, Wit AL, Hoffman BF. Genesis of cardiac arrhythmias. Circulation 1973; 47:190–204.
14. Cranefield PF, Wit AL, Hoffman BF. Conduction of the cardiac impulse. III. Characteristics of very slow conduction. J Gen Physiol 1972; 59:227–246.
15. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology. The Sicilian Gambit: a new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Circulation 1991; 84:1831–1851. (Simultaneously published in Eur Heart J 1991; 12:1112–1131.
16. An R-H, Bangalore R, Rosero SZ, Kass RS: Lidocaine block of LQT-3 mutant human Na^+ channels. Circ Res 1996; 79:103–108.
17. Schwartz PJ, Priori SG, Locati EH, Napolitano C, Cantù F, Towbin JA, Keating MT, Hammoude H, Brown AM, Chen L-S K, Colatsky TJ. Long QT syndrome patients with mutations of the *SCN5A* and *HERG* genes have differential responses to Na^+ channel blockade and to increases in heart rate. Implications for gene-specific therapy. Circulation 1995; 92:3381–3386.
18. Lue WM, Boyden PA. Abnormal electrical properties of myocytes from chronically infarcted canine heart. Circulation 1992; 85:1175–1188.
19. Sicouri S, Antzelevitch C. A subpopulation of cells with unique electrophysiological properties in the deep subepicardium of the canine ventricle: the M cell. Circ Res 1991; 68:1729–1741.
20. Members of the Sicilian Gambit. Antiarrhythmic therapy: a pathophysiologic approach. Armonk NY: Futura Publishing Co., 1994.
21. Vaughn-Williams EMA. Classification of antiarrhythmic actions reassessed after a decade of new drugs. J Clin Pharmacol 1984; 24:129–147.
22. Harrison DC. Antiarrhythmic drug classification: New Science and practice applications. Am J Cardiol 1985; 56:185–187.

Grand Rounds

The Acute Treatment of Supraventricular Tachycardia

Marie Noelle S. Langan, M.D.

Abstract

The diagnosis of supraventricular tachycardia has become much more important with the advent of radiofrequency ablation. This is usually best done at presentation in an acute setting. A 12-lead electrocardiogram should be a routine aid in making the diagnosis. A continuous rhythm strip must be obtained during administration of adenosine and at the termination of tachycardia. Most recent treatment guidelines would include adenosine as first-line therapy. If adenosine fails to restore normal sinus rhythm, diltiazem or a beta blocker should then be considered. If there is significant heart failure, digoxin may be useful. In the presence of wide complexes, agents that produce atrioventricular nodal block should be avoided.

Before the 1980s "supraventricular tachycardia" was a term used to describe any arrhythmia originating above the ventricle and was a sufficiently precise diagnosis in most cases. With the advent of new medications and particularly radiofrequency ablation, finding the mechanism of the supraventricular tachycardia has gained significance. In clinical practice, this is best done when the patient presents with the arrhythmia, either in the emergency room or in the physician's office. Primary care physicians therefore have a new and important role in treating patients with supraventricular tachycardias.

In general, there are three mechanisms for arrhythmias: triggered, automatic, and reentrant. This applies equally to supraventricular and ventricular arrhythmias. In classifying supraventricular arrhythmias it is often easiest to combine mechanism with anatomy. Thus, from the upper chamber to the atrioventricular (AV) node, the possibilities are sinus reentrant tachycardia and (automatic) sinus tachycardia. In the atrium there is automatic atrial tachycardia, multifocal atrial tachycardia (probably a triggered rhythm), intra-atrial reentrant tachycardia, and atrial flutter and fibrillation (most likely reentrant rhythms). At the AV node the most common arrhythmia occurs, AV nodal reentrant tachycardia, and also junctional tachycardia, an automatic rhythm. Finally, when an abnormal accessory pathway is present AV reentrant tachycardia occurs (Fig. 1). An aberrantly conducted impulse through the HIS Purkinje system, or an infrequently occurring antidromic AV reentrant impulse which descends through the bypass tract and back up the AV node can cause a wide QRS complex in the electrocardiogram and can be seen in supraventricular tachycardia. If the rhythm is irregular, the underlying cause may be atrial fibrillation with aberrant conduction via a bypass tract.

Supraventricular tachycardias can be differentiated by several methods:

- clinical evaluation
- a 12-lead electrocardiogram
- vagal maneuvers and response to adenosine.

It is important to define the underlying mechanism responsible for the tachycardia to evaluate the risks and choose the most appropriate therapy.

In general, automatic rhythms are more commonly related to underlying disease, especially

---

Address reprint requests to M. Noelle Langan, M.D., Assistant Professor of Medicine, Division of Cardiology, Department of Medicine, The Mount Sinai School of Medicine, Box 1030, One Gustave L. Levy Place, New York, NY 10029.

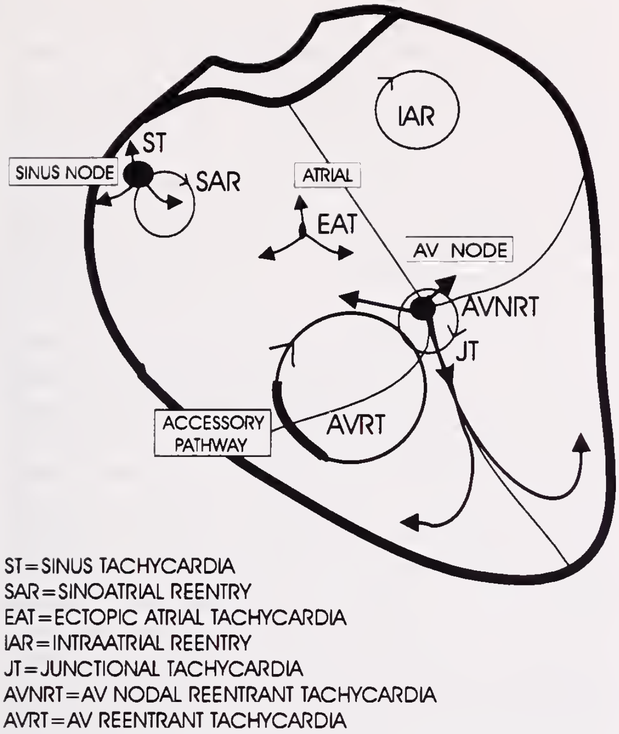

IAR
ST
SINUS NODE
SAR
ATRIAL
EAT
AV NODE
AVNRT
JT
ACCESSORY PATHWAY
AVRT
ST=SINUS TACHYCARDIA
SAR=SINOATRIAL REENTRY
EAT=ECTOPIC ATRIAL TACHYCARDIA
IAR=INTRAATRIAL REENTRY
JT=JUNCTIONAL TACHYCARDIA
AVNRT=AV NODAL REENTRANT TACHYCARDIA
AVRT=AV REENTRANT TACHYCARDIA

Fig. 1. Mechanisms of supraventricular tachycardia. The differential diagnosis for supraventricular tachycardia is illustrated in terms of anatomical source and mechanisms possible at each location (automatic versus reentrant).

pulmonary disease. Atrial fibrillation often is a late occurrence in patients with coronary disease. Other illnesses such as thyroid disease and infections may be associated with atrial fibrillation. The age at onset of the tachycardia, however, is not particularly helpful in determining the diagnosis. Occasionally, an arrhythmia may occur with drug toxicity, particularly with theophylline and digitalis which may cause automatic rhythm and triggered junctional rhythms, respectively.

Obtaining a 12-lead electrocardiogram during the tachycardia is crucial to making the diagnosis (1). The data suggest that the origin of the tachycardia can be determined by the electrocardiogram in more than 80% of the cases in which the QRS complex is narrow. The first rule in interpreting the electrocardiogram is to locate the P waves. If P waves are not seen, the tachycardia is most likely to be AV nodal reentrant tachycardia if the rhythm is regular (Fig. 2d) and atrial fibrillation if the rhythm is irregular (Fig. 2g). AV nodal reentrant tachycardia is also heralded by the presence of an RSR′ in Lead V1 which is not seen on the electrocardiogram during sinus rhythm. The R′ of Lead V1 is in fact a P wave occurring close to the QRS (Fig. 2e).

If P waves are clearly seen, the tachycardia can be classified further into one or another group depending on whether the duration of the PR interval is shorter than the duration of the RP interval. The former case suggests the mechanism of the tachycardia is confined to the sinus node or atria. If the morphology of the P wave is similar to that seen in sinus rhythm (a positive P wave in Leads I, II, III, AVL, and AVF), then the tachycardia most likely originates in or close to the sinus node (Fig. 2a). If, on the other hand, the P wave morphology differs from that seen in sinus rhythm, then either an intra-atrial reentrant tachycardia or automatic atrial tachycardia is most likely (Fig. 2b). If several differently shaped P waves are seen, the atrial tachycardia is considered to be multifocal (Fig. 2c).

The other group consists of those cases in which the RP interval is shorter than the PR interval. This suggests that the impulse is using a rapid retrograde pathway. The most common tachycardia with this morphology is the typical form of AV nodal reentrant tachycardia, but about one third of these AV reentrant tachycardias use a bypass tract (Fig. 2f). Both of these

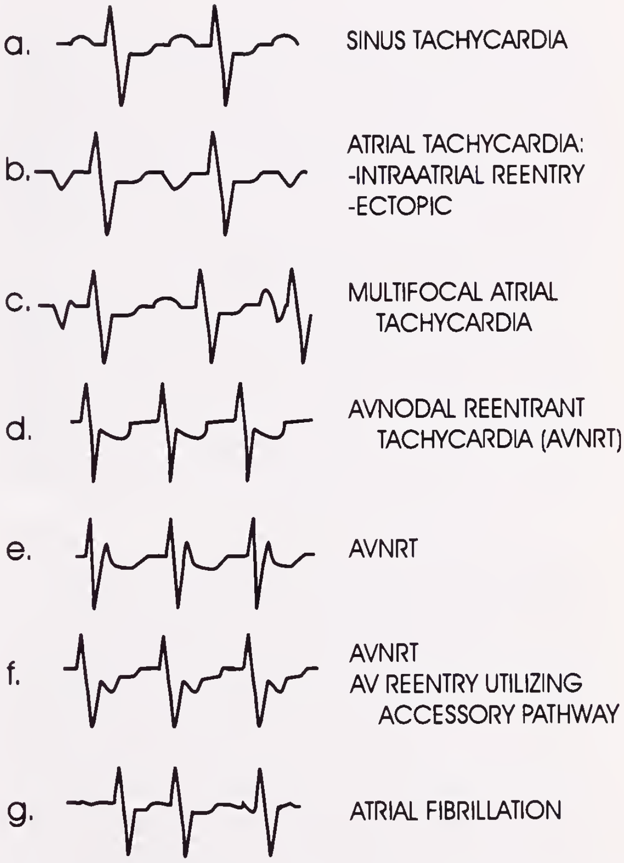

a.
SINUS TACHYCARDIA
b.
ATRIAL TACHYCARDIA:
-INTRAATRIAL REENTRY
-ECTOPIC
c.
MULTIFOCAL ATRIAL TACHYCARDIA
d.
AVNODAL REENTRANT TACHYCARDIA (AVNRT)
e.
AVNRT
f.
AVNRT
AV REENTRY UTILIZING ACCESSORY PATHWAY
g.
ATRIAL FIBRILLATION

Fig. 2. Typical electrocardiographic tracings from lead V_1. P waves and their relationship to the QRS complexes are shown. (a–c) examples of tachycardias in which the PR interval is less than the RP interval; (d, e) examples in which no obvious P waves are visible (note in e the pseudo R′ which is in fact a P wave); (f) an example in which the RP interval is less than PR interval; (g) an example of irregular rhythm and tachycardia caused by atrial fibrillation.

forms of reentrant tachycardias require a competent AV node for the circuit to continue. Thus, those tachycardias with a short RP would be expected to terminate if the AV node was blocked. In studies defining the mechanism of supraventricular tachycardias it has been shown that nearly 85% are AV node dependent. This is important because these tachycardias should all terminate with adenosine (2).

Adenosine is a naturally occurring substance with a very short half-life. It is constantly being produced and metabolized by all cells in the body. Adenosine alters the properties of potassium and calcium ion channels to slow conduction and prolong the refractory period in the AV node. Thus all tachycardias using the AV node as an essential part of their circuit (short RP interval) should be terminated in response to the administration of adenosine in contrast to those with short PR intervals. In the latter instance, although the ventricular response may slow in response to adenosine, the underlying cause of the tachycardia remains unaffected. Recent data suggest that, contrary to early reports, some atrial tachycardias caused by a triggered mechanism may be terminated after adenosine. However, AV block is often seen for a beat or two before termination, suggesting the diagnosis. Therefore the administration of adenosine is important both in its ability to treat the arrhythmia as well as in helping to define the mechanism. It is vital to obtain rhythm strips at the time of adenosine administration.

Important facts to remember regarding adenosine are: its half-life is very short, it is metabolized and degraded en route to the heart, and it must reach the coronary circulation to be effective. It is imperative to use a large vein to administer adenosine and to follow the administration of adenosine with a bolus of normal saline.

Recent guidelines suggest that 6 mg of adenosine may be given intravenously followed by 12 mg if necessary. If there is no effect within 5 minutes, because the half-life of adenosine is less than a minute, a second bolus can be given. If there is no effect with 12 mg, the adequacy of the intravenous line and the flushing technique should be evaluated. If a central line is to be used to administer the adenosine, the initial dose should be reduced by half because the concentration of the drug delivered to the heart may be much higher than that delivered via a peripheral vein. It is important to know that adenosine is antagonized by theophylline which binds to the same receptor. The effect of adenosine is enhanced by dipyridamole. Promoting vagal activity or tone with a Valsalva maneuver or carotid sinus massage may also block the AV node, but adenosine therapy essentially performs the same role. If the acute arrhythmia has not been terminated by promoting vagal tone or by appropriate administration of adenosine, or if adenosine administration results only in temporary slowing of the ventricular rate, a more prolonged AV nodal blocker should be used. The options fall into three categories: beta blockers, calcium channel blockers, and digoxin.

Intravenous digoxin has lost favor recently because of its lack of effectiveness in acute therapy of supraventricular tachycardia. It has two major problems. The first is that its mean time to action ranges from 2 to 5 hours (3). This makes it less desirable in an emergency. Second, its primary electrophysiologic actions are mediated by its vagotonic effect, the direct block of the AV node being secondary to a weak effect on Mg/ATPase. In the setting of supraventricular tachycardia in which sympathetic levels are markedly elevated, it is less likely to block the AV node and decrease the ventricular rate. As a result, other intravenous AV nodal blockers have become more popular.

Diltiazem administered intravenously is a specific calcium channel blocker which directly affects conduction through the AV node. Its time to action is approximately 15 minutes. When administered as an appropriate intravenous bolus (0.25 mg/kg) followed by continuous intravenous drip, its ability to block the AV node is in the 90% range. If the first bolus is ineffective a second bolus in the range of 25 mg should follow 20 to 30 minutes later. A frequent reason for lack of efficacy is the failure to follow the bolus injection with the intravenous drip or to give a second bolus for up to 2 hours. Of note, unlike adenosine, although its action is rapid, diltiazem does take a considerable time to leave the circulation completely. In controlled studies of ventricular response in atrial fibrillation, a bolus of diltiazem followed by a placebo intravenous drip demonstrated an effect for up to 20 hours (4). It is therefore vital to determine whether there are any contraindications to diltiazem before this first bolus. Major contraindications are very poor ejection fraction, hypotension, a previous history of serious sick sinus disease, and/or AV nodal block. Although it is unlikely, a patient who is experiencing a rapid ventricular response may convert to sinus rhythm with complete heart block. Therefore, a prior history of arrhythmias, if available, should be reviewed. Diltiazem does cause some vasodilation and negative inotropy. However, slowing the ventricular rate may allow for an increase in stroke volume. In some patients, an increase in stroke volume and perhaps cardiac output might compensate for some degree of vasodilation with little or no change in mean blood pressure. A most troubling situation may occur in a patient with atrial fibrillation who has only a moderate ventricular rate (120–130 bpm) and a very bad ejection fraction. In this case, the vasodilation and decreased contractility may result in reduced cardiac output and significant hypotension. This is the group of patients in which digoxin is probably preferable as the first line of therapy.

Because intravenous beta blockers recently have become available, their use now can be considered in the acute setting. Although bronchoconstriction and diminished myocardial contractility may be seen as adverse reactions, these agents have a more rapid onset and shorter duration than diltiazem.

The most feared supraventricular tachycardias are those that are related to Wolff-Parkinson-White Syndrome. Unless there is a history and/or an old electrocardiogram available, this underlying abnormality may not be evident at the time of presentation of the tachycardia. As discussed above, a *narrow* complex tachycardia using a bypass tract must be orthodromic (the impulse must go down the AV node and up the bypass tract). Adenosine will cause AV nodal block and terminate the tachycardia. The only danger in this setting is that administration of adenosine may convert a supraventricular tachycardia to atrial fibrillation. The onset of atrial fibrillation in a patient with Wolff-Parkinson-White Syndrome may result in ventricular fibrillation because the existing bypass tract may be capable of rapidly conducting and delivering these impulses directly to a small focus in the ventricle. Ordinarily, preserving conduction through the AV node in atrial fibrillation would be desirable because the ventricle would remain refractory to aberrant stimuli from other loci (**Fig. 3**). Therefore, any increase in AV node block with adenosine would enhance the chance of ventricular fibrillation. Because of the short duration of action of adenosine, this outcome is very unlikely. However, the prolonged duration of action as seen with diltiazem or digoxin would entail more risk. Thus, patients with wide complex arrhythmia should be treated with either direct cardioversion or with pronestyl which blocks the bypass tract and may convert the atrial fibrillation.

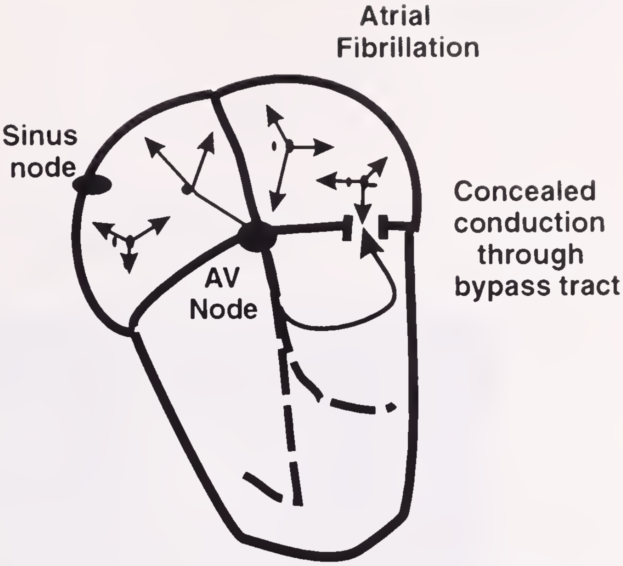


Fig. 3. Illustration of conduction to the ventricle during atrial fibrillation in a patient with Wolff-Parkinson-White Syndrome. Note that fibrillatory waves are conducted both through the AV node and the bypass tract antegrade and retrograde allowing for some concealed conduction into the bypass tract after ventricular excitation by the AV node.

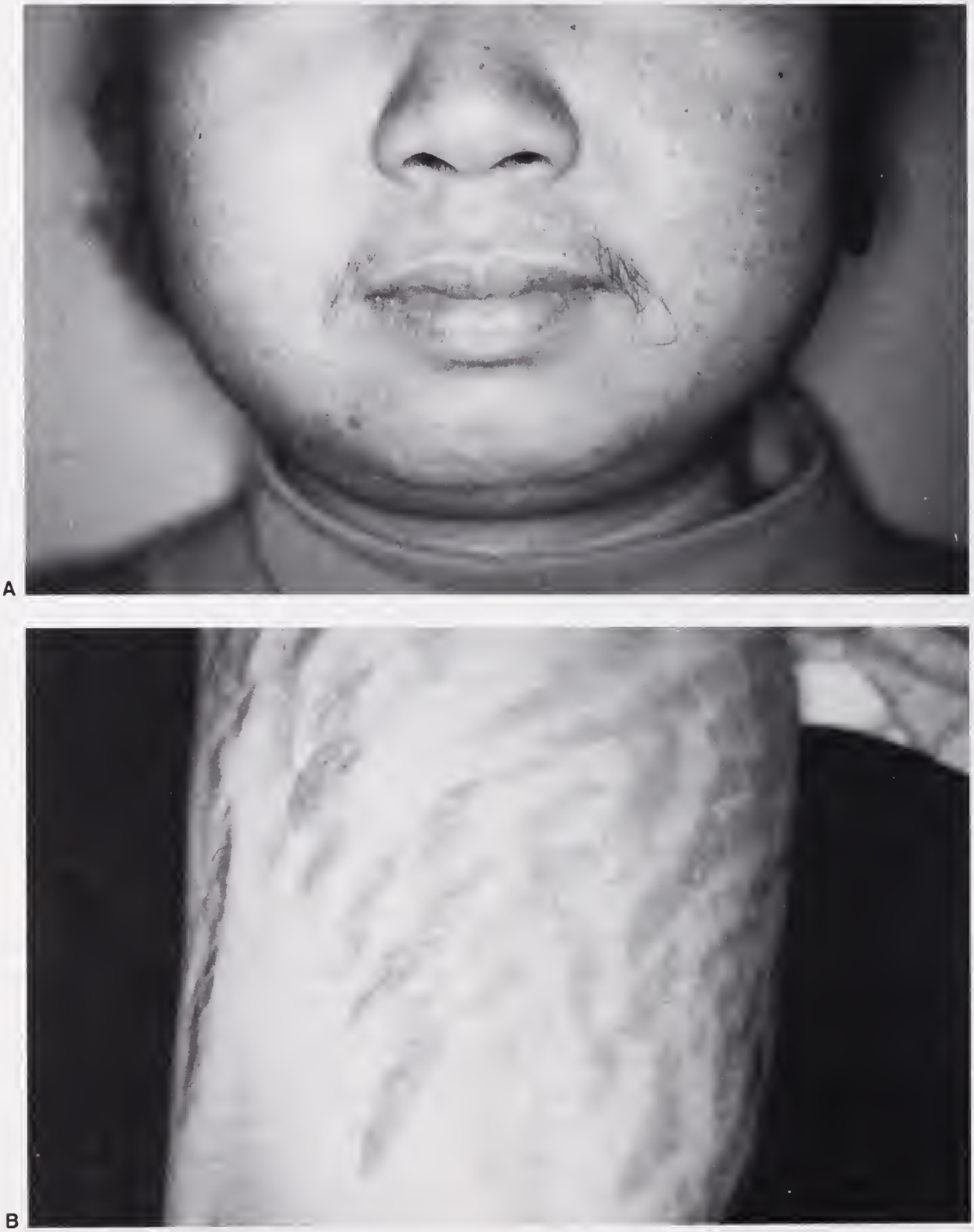
In summary, the diagnosis of supraventricular tachycardia has become much more important with the advent of ablation. In the acute setting, a 12-lead electrocardiogram should be routine. A continuous rhythm strip must be obtained during the administration of adenosine and at the termination of the tachycardia. As for treatment, except as noted, adenosine should be the first line therapy. If adenosine fails to cause reversion to sinus rhythm, diltiazem or intravenous administration of a beta blocker should then be considered. If there is significant heart failure, digoxin may be useful as first line of therapy. In the presence of wide complexes, agents which enhance AV nodal block should be avoided.

References

1. Kalbfleisch SJ, El-Atassi R, Calkins H, Langberg JD, Morady F. Differentiation of paroxysmal narrow QRS complex tachycardias using the 12-lead electrocardiogram. J Am Coll Cardiol 1993; 21:85–89.
2. Rankin AC, Brooks R, Ruskin JN, McGovern BA. Adenosine and the treatment of supraventricular tachycardia. Am J Med 1992; 92:655–664.
3. Falk RH, Leavitt JI. Digoxin for atrial fibrillation: a drug whose time has gone? Ann Intern Med 1991; 114:573–575.
4. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. A placebo-controlled trial of continuous intravenous diltiazem infusion for 24-hour rate control during atrial fibrillation and atrial flutter: a multicenter study. J Am Coll Cardiol 1991; 18:891–897.

Dermatology Notes

Cushing's Syndrome



Iatrogenic Cushing's syndrome. Note the characteristic moon faces in A and purple striae in B in a patient taking high-dose systemic steroids.—*Neal Schultz, M.D., and Mark Lebwohl, M.D.*

Book Reviews

Future Practice Alternatives in Medicine

David B. Nash, New York and Tokyo: IGAKU-SHOIN, 1993. 2nd ed., 408 pp, index, $24.50. ISBN 0-89640-236-3.

The first edition of this book was published in 1985. The second edition has been completely rewritten and might well be entitled, "A Compendium to Future Medical Practice Alternatives." The content is broad and includes knowledgeable reviews of professional development, education, and practice in a changing society in which markets, medical care delivery, and politics are increasingly driving future directions of the profession. It is likely that, similar to students desiring subspecialty information, readers will be selective and seek information appropriate to their needs. For such individuals this text is strongly recommended. It is well written, easy to understand, and filled with helpful and provocative information. It is an especially useful guide for the young student and physician in his formative years.

In the preface the author contends that the medical career is a series of disjointed periods which follow college, producing a maturing physician ill prepared for the changes occurring in our society. It is suggested that a more meaningful educational transition occurs during levels of training and practice so that what is exported at residency completion better matches both the goals of the student and the needs of society.

The book is divided into three sections and an overview. Sixteen contributors have combined their talents in a broad review of analyses of the current and future directions of the medical profession. Although published in 1993, the subjects remain up to date, the reviews pertinent, and the projections valuable to the reader.

In his overview, "White Coat or Blue Collar," Dr. Nash, who is both a physician and an MBA and is currently the Director of Health Policy and Clinical Outcomes at Jefferson Medical College, points out that although clinical training for the skills and understanding of decisions for diagnosis and medical management of disease is well developed, satisfaction in providing cost-effective care, understanding of economics of care, outcomes, delivery systems, quality assurance, dealing with errors, and leadership roles are minimal or lacking. The overview addresses these issues and outlines the current economic environment, physician surplus, and general trends in the nature of practice. The latter emphasize practice by protocols, changing professional and patient relationships, vulnerability of specialties, growth of group practice, changes in funding of graduate medical education, and shifts of political power from providers to payers of health care.

After the overview, the first section is entitled "Social Concerns" and consists of four chapters. In the first Drs. Barry L. Liebowitz and Dr. Donald C. Meyer review physician collectivism and suggest that current trends may force physicians to organize in ways they have not considered recently. Their provocative essay is followed by the thesis developed by Dr. David J. Brailer that physicians should act as agents of social change and should influence politics that are beneficial for their patients. Dr. James C. Couch outlines five types of physicians required to shape the future of medical practice. These include diehards, groupies, entrepreneurs, Reaganites, and what he describes as the "New Breed." The section concludes with Dr. Lila Stein Kroser's well-written report on women in medicine. The trends for women and the conflicts they face are poorly recognized and often little understood. Dr. Stein reviews the growing influence of women physicians, styles of practice, organization, and balance of work and home responsibilities. Women beginning a career in medicine are well advised to review this chapter.

The second section reviews "Emerging Career Trends" in six separate chapters. In the first, Dr. Risa Lavizzo-Mourey analyzes differences between internists and geriatricians, outlines the knowledge and the art, and speculates on the future of geriatric medicine. Dr. David Gluck reviews occupational health and corporate medical directors as a potential subspecialty; Drs. Seth A. Rudnick and Alan S. Rosenthal then discuss physician executives in the pharmaceutical industry and their impact on academia. These essays are followed by a review of medical directors of health maintenance organizations by Drs. Thomas James, III and David Nash and by reported insights into managing health care delivery systems in an academic environment by Drs. Robert Hodge and David Nash. Finally Dr. Robert Taylor reviews primary care and family practice and discusses "survival skills" necessary for the primary care giver.

The final section of the book in entitled "Future Directions." The first chapter, written by Dr. Jay B. Krasner, describes the history of computers in medicine and speculates about their future trends. The second essay, written by Dr. Allan Douma, uses generic criteria to help readers evaluate programs of continuing medical education. Finally, Drs. S. Alan Hillman and A. Mark Fendrick complete the last chapter which they entitle the "Technologic Imperative." They outline the need for cost benefit and cost effectiveness analyses as methods for technology assessment of new discoveries.

Stanley Reichman, M.D.
Mount Sinai School of Medicine

The Physician's Guide to Managed Care

David B. Nash. Gaithersburg, MD: Aspen Publication, 1994. XVI and 248 pp, $65.00. ISBN 0-8342-0393-6

THIS MULTIAUTHORED, EDITED BOOK, written by physicians for physicians, attempts to assist the reader to understand the challenges of a world increasingly altered and dominated by managed care. The definition of managed care provided in the book's foreword sets the tone for the entire book, "Managed care is the process of the application of standard business practices to the delivery of health care in the traditions of the American free enterprise system."

Clearly, managed care is cost driven and not care driven. The term itself is a euphemism for converting medical decision making into business decision making, thereby controlling and containing costs. Most managed care advocates have business backgrounds rather than clinical experience. In fact, most of the nine chapters in this book are written by physician administrators rather than practicing physicians.

The book presents an overly optimistic view of managed care, minimizing its problems. The physician-patient relationship is spoken of in glowing terms, whereas in reality this relationship may be seriously threatened as physicians are asked to serve as "double agents weighing competing allegiances to patients' medical needs against the monetary costs to society" (Angell M. Kennedy Inst. Ethics J. 1993; 3:279).

The term managed care may in fact be an oxymoron because "care" requires flexibility and judgment, whereas "managed" implies rigidity and rules. Managed care thus intrudes on and limits physician autonomy. Managed care offers certain options but the one desired by the physician or patient may not be one of those offered. Physicians and patients may not even understand the exclusions, limitations, and gatekeeping aspects of HMOs. The art of medicine should still take precedence over the business of medicine. *The Physician's Guide to Managed Care* minimizes these and other problems or discusses them only very briefly in passing.

The overview chapter mentions medical education and national health reform but fails to address who will pay for undergraduate and graduate medical education under managed care. The chapter detailing the average life of the HMO physician presents an extremely rosy and optimistic view emphasizing the pros and glossing over the cons. Problems of gatekeeping are acknowledged in the chapter on ethical issues but minimized. Other problems which are barely, if at all, mentioned include underprescription of services, lack of free choice, concern about restraint of trade, physician and/or patient incentives, the ability of primary care physicians to control use of medical care, the limited information on cost-effective medical practice, the selection or rejection of physicians by managed care companies, and gatekeepers treating patients beyond their training or competency instead of timely referral for consultation. Good primary care internists, pediatricians, and family practitioners are being forced to take on the role of being mediocre specialists.

The rapidly changing health care reform scene sweeping the United States makes a book like this out of date before it is even published. References at the end of each chapter are only up to 1992, and the entire debacle of the 1993 Clinton health care reform proposal is not cited at all. The chapter on leadership offers a comprehensive account of the types of management and leadership roles for physicians in managed care and the skills needed for physicians who choose such a career. The chapter on the National Association of Managed Care Physicians (NAMCP) provides a good brief history of managed care and the formation, function, and future of the NAMCP. The authors seem to be making a strong sales pitch for their organization.

The chapter on cost effectiveness is very long (many of the "busy" tables and case studies are superfluous) but easy to understand. "Selective credentialling" (page 125) raises serious moral issues which are not discussed. Only one paragraph is devoted to practice guidelines, yet three pages discuss preoperative laboratory evaluation. The chapter entitled "The Centers for Excellence Phenomena" is a euphemism for the bundling of costs (page 161) or the packaging of prices (page 173) for very expensive services such as open heart surgery or organ transplants. The listing of only seven institutions (page 176) which participate in national organ transplantation networks is very misleading and can be interpreted as a commercial advertisement for those institutions. The chapter on case mix systems reads like a lecture converted to writing. The last chapter describes the role of managed care in future health care policy proposals.

In summary, this book is well written and reads easily, but it emphasizes the "managed" and deemphasizes the "care" part of the term managed care. Education, research and the place of academic medicine in a managed care environment are not discussed. The book deals primarily with pragmatic economic concerns. Patients are viewed as consumers and the patient-physician encounter as a market arrangement. This book is a good sales pitch for managed care companies and might be distributed as required reading to their physicians (or those comtemplating employment with them), free of charge. (The book sells for $65.)

Fred Rosner, M.D., F.A.C.P.
Mount Sinai Services
Queens Hospital Center and
Mount Sinai School of Medicine

AHCPR95-0644. Understanding Acute Low Back Problems. Consumer Version. No. 14, 14 pp. AHCPR95-0643. Acute Low Back Problems in Adults. Quick Reference Guide for Clinicians. No. 14, 29 pp. AHCPR95-0642. Acute Low Back Problems in Adults. Clinical Practice Guideline. No. 14; 168 pp.

Bigos S, Bowyer O, Braen G, et al. Agency for Health Care and Policy Research.

The U.S. Department of Health and Human Services (DHSS) and the Agency for Health Care Policy and Research (AHCPR) recently released three publications on acute low back problems in adults: a consumer version, a quick reference guide for clinicians, and a clinical practice guideline. The goal of the multidisciplinary panel of 23 private-sector clinicians and other experts was to outline state-of-the-art recommendations and treatment.

In providing these three publications, the DHSS and AHCPR take on a health problem that affects almost everyone at some point in their lives, accounts for 1% of the chronically disabled in the United States and another 1% of the temporarily disabled, and costs health care providers between $20 and $50 billion annually. The safest effective medication is acetaminophen, followed by nonsteroidal antiinflammatory drugs. No additional benefits are ascribed to muscle relaxants, opioids, oral steroids, colchicine, or antidepressant medications. Invasive procedures, such as trigger point injections with local anesthetic, epidural, or facet joint injections with steroids, and acupuncture are not recommended.

Initial assessment should focus on indicators of potentially serious spinal or nonspinal pathology; in the absence of "red flags," further testing is not necessary during the first 4 weeks. Relief of discomfort can be accomplished most safely with nonprescription medication and/or spinal manipulation. Strict bed rest over 4 days is not helpful; stretching maneuvers may begin during the first 2 weeks, followed by conditioning exercises for trunk muscles. Patients recovering from acute low back problems are encouraged to return to work; in cases of continuing sciatica and persistent low back symptoms, imaging studies such as computerized tomography and magnetic resonance imaging may be appropriate after 1 month. Neurosurgical intervention may be considered after 4 weeks; standard discectomy and microdiscectomy are more efficacious than chymopapain injection or percutaneous discectomy. With or without surgery, 80% of patients with sciatica recover eventually; psychological and socioeconomic problems influence expectations for recovery.

Chiropractic care and spinal manipulation are found to be helpful during the first 4 weeks. Other methods of symptom control, including transcutaneous electrical nerve stimulation, shoe inserts, lumbar corsets, spinal traction, and biofeedback, have not proven beneficial. Computerized tomography and magnetic resonance imaging findings must be interpreted with the entire clinical picture for neurosurgical evaluation. Other diagnostic studies, such as plain x-rays, bone scan, or electromyography, may be indicated in the presence of "red flags" when tumor or infection or fracture is suspected. Discography does not meet the criteria as efficacious.

The Consumer Version helps the patient understand acute low back problems. Treatments that have proven to relieve symptoms are recommended, and unsuccessful modalities of therapy are identified. The low incidence (1 in 200) of people who have dangerous conditions requiring immediate intervention is stressed. In an age when physicians in private practice and doctors in health maintenance organizations have limited time for initial evaluation, the pamphlet provides an unhurried review of various aspects of the condition.

The Quick Reference Guide for Clinicians gives the practitioner guidelines for assessment, diagnostic studies, and treatment. In the evolving world of medicine with its heavy dependence on health maintenance organizations, the DHSS and the AHCPR may have inadvertently provided the criteria for minimal evaluation and management. Cost effectiveness seems an absolute goal.

The Clinical Practice Guideline additionally distinguishes stenosis, spinal instability, and spondylosis from herniated lumbar discs. Appropriate neurosurgical intervention is discussed. Advancements in technology and technique not reviewed by Bigos, Bowyer, Braen, et al. are now recording that percutaneous endoscopic discectomy is equaling the results of standard laminectomy and microdiscectomy. Overall, the Guidelines is a worthwhile update on treatment for the neurologic, neurosurgical, or orthopedic specialist.

Martin H. Savitz, M.D.
Mount Sinai School of Medicine

Information for Authors

THE MOUNT SINAI JOURNAL OF MEDICINE, established in 1934 as *The Journal of the Mount Sinai Hospital,* is a peer-reviewed general medical journal. It is indexed or abstracted in *Index Medicus, Current Contents, Science Citation Index, Hospital Literature Index, International Nursing Index, Excerpta Medica, Chemical Abstracts, Biological Abstracts,* and major databases. Theoretical and basic science articles for the clinician, reviews, reports of clinical or research experience, articles on any subject affecting the practice of medicine, short notes in any specialty, book reviews, letters, and articles by medical students are welcome. The *Journal* generally follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals as revised in 1997 and modified by *The Journal* to conform to the style employed by it. The *Journal* aims at responding to authors of manuscripts within 8 weeks of submission.

Communications. Manuscripts and correspondence should be addressed to: Editor, *The Mount Sinai Journal of Medicine,* The Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Phone: (212) 241-6108; FAX: (212) 722-6386; e-mail: msjournal@msvax.mssm.edu.

Authorship Responsibility, Financial Disclosure, and Assignment of Copyright. Each author is required to sign (1) the statement on authorship responsibility; (2) the statement on financial disclosure; and (3) either the statement on copyright transfer or (4) the statement indicating that the author is or was a US government federal employee when this work was conducted and prepared for publication. These statements are printed from time to time on a page in the *Journal* entitled "Required Form for Authors" and can be photocopied for use. Copies may also be obtained from *The Journal's* office. Use additional copies of the form if there are more than six authors, and replace with the appropriate number of the author, e.g., 7th, 8th, etc. The signed original form(s) should be submitted with the manuscript.

Manuscript Preparation. Submit manuscripts in triplicate, including three sets of illustrations (see below). **Manuscripts must be typewritten or computer generated, double spaced throughout (including references, legends, and tables),** on one side of 8½ × 11 inch white bond paper with **one inch** margins. Other than the Title Page, the abstract page and each page containing text, legends, or tables should be numbered sequentially in the **top right corner,** and include a heading or header which identifies the last name of the first author in the **top left corner.** Begin a new page for the title page, abstract, initial page of text, references, each table, and legends. A floppy disk, if available, should accompany the manuscript. The label on the disk should specify the name of the first author, the title of the manuscript, how the disk has been formatted, and the word processing system used (DOS, Windows, or Windows 95). PC format is preferred but a high-density formatted Macdisk is acceptable. The text should be in ASCII, Microsoft Word or Wordperfect.

Drugs must be identified by their generic names. Do not use abbreviations on the title or abstract page. Define all abbreviations on first use in the body of the manuscript.

Any material taken directly from other sources must be accompanied by a written statement from both the author and publisher giving permission to *The Journal* for reproducing it. The authors must document in the manuscript that all clinical investigations described in the manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board or its equivalent. The text must indicate that the informed consent of each subject was obtained. If results of experiments on animals are reported in the manuscript, the text must indicate that these studies were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office or its equivalent which supervises such work.

Title Page. The title page must be double spaced, and not numbered. It should indicate (1) title of the article, phrased as concisely as possible; (2) first and last name of each author, middle initials, if any, and not more than two academic degree(s); (3) institutional affiliation and title or rank of each author; (4) name and address of department(s) and institution(s) from which the work originated; (5) the name and address (and voice and FAX telephone numbers if available) of the author who will receive and respond to correspondence; (6) the name and full postal address of the author from whom reprint(s) are to be requested; (7) acknowledgments of sources of grant support; (8) name, place, and date of any conferences at which some or all of the information was presented; and, (9) a running head of fewer than 40 letter spaces. At the bottom of the title page, *list 3 to 10 key words or phrases* to facilitate indexing in accord with Medical Subject Headings from Index Medicus. If more than one sheet is needed, label the supplemental sheet as Title Page ii.

Abstract. All articles must include an abstract on the first numbered page of the manuscript of not more than 250 words. Abstracts should be double spaced and divided into four paragraphs:

Background: what problem(s) was(were) addressed;
Methods: how the study was performed;
Results: the salient results;
Conclusions.

Key Words. Three to 10 key words or phrases must be provided at the bottom of the title page to facilitate indexing. (see above)

Units of Measurement. SI units are preferred, but values may be expressed in conventional units and conversion factors indicated. The range of normal values for the reporting laboratory must be indicated. When conventional units are used in figures or tables, the appropriate conversion factor(s) must be provided in legends or footnotes.

Editing. All papers will be edited to enhance conciseness and clarity without altering meaning and to ensure conformity with journal style. Authors whose primary language is not English should obtain help from someone proficient in English spelling and grammar.

Illustrations. Photographs, line drawings, and graphs should enhance understanding of the text. Three copies of each must be submitted with the manuscript. Line drawings and graphs should be professionally prepared or computer generated and camera ready. Symbols, lettering, and numbers should be large enough to remain easily legible after the figure has been reduced to fit the width of one column. Photographs must be sharp, high contrast, black and white glossy prints not exceeding 5 inches in height × 7 inches in width. The authors must pay attention to the quality of print reproductions of x-ray plates or transparencies to assure that the special features are labeled and will remain easily visible when reduced to fit the width of one column. The name of the subject and hospital number(s) should not be reproduced in the print. Black and white copies of photomicrographs are preferred and must be cropped to a width of 3⅛ inches. The type of stain and power of magnification must be indicated in the relevant legend. Electron photomicrographs should have internal scale markers. On the back of each print and photograph affix a gum label on which the number of the figure has been written to correspond to its identification in the text, title of manuscript, first author's last name, and the word "top" and arrow to indicate the top edge. **Do not write this information directly on the print and do not mount the print on cardboard.** Illustrations which are to appear together should be mounted accordingly as plates and should be equally sized. Protect the prints by enclosing them in cardboard and separate envelopes. **Do not use paper clips.**

Every effort should be made to avoid using a photograph which includes the face or part of the face of a subject. Facial

features should be marked to prevent identification of the subject unless the illustration carries details absolutely essential to the text. In any case, a partial or full facial photograph of a subject will not be published unless written permission has been obtained from the subject and accompanies the photograph.

Legends. Legends should not duplicate the text. Each should be on a separate sheet of paper and double spaced. Number each legend to match the illustration it describes. Illustrations mounted as plates to appear together should be accompanied by a single legend identifying the separate elements by position ("upper left," "middle") or by letters. If such illustrations have been labeled with letters, the same letters are to be used in the legend. The legend must indicate the magnification and type of stain used for photomicrographs.

Tables. Each table should be typed on a separate page, double spaced. Number tables consecutively (Table 1, etc.) to correspond to their appearance in the text. Give each table a brief title that is self-explanatory without reference to the text and type the title on a separate line below its number. Identify all abbreviations and/or symbols used in the table in a footnote.

References. All references cited in the text are to be numbered sequentially. Enclose the citation number in parentheses and place it before any punctuation, e.g., Cytomegalovirus (1), steroids (2,3), and recreational drugs (4–6) have all been implicated (7). Do not use superscripts. The reference list must be limited to works cited in the text, and numbered in the order in which they are cited. Journal title abbreviations must conform to those used in *Index Medicus*. The styles to be used for various kinds of citations to be listed in the section of the manuscript entitled References are illustrated in the version of "Uniform Requirements" published in the New England Journal of Medicine referenced below. The list of references must be typed, double spaced, on separate pages, following the arrangement and punctuation style as shown in the examples.

1. Brown LK. Sleep apnea syndromes: overview and diagnostic approach. Mt Sinai J Med 1994; 61:99–112.
2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336(4):309–315.
3. Couser WG. Glomerular diseases. In: Stein J. ed. Internal Medicine 2nd ed. Little Brown: Boston, 1987: 834–861.

List the names of all authors when there are four or fewer. When there are five or more, list the names of the first three, then *et al.*

References to unpublished data (unless the information is In press) and personal communications should not be included in the list of numbered references. Instead, such information should be placed in the text in parentheses. Permission must be obtained from the appropriate individual to so quote the material. This permission must accompany the manuscript at the time of its submission. If the manuscript is accepted for publication, the author(s) will be asked to confirm the accuracy of all references.

Proofs. Proofs will be sent to the corresponding author as soon as they are available. Stylistic changes should not be made. Because of increased printing charges, the cost of author's alterations beyond routine correction of typographical errors in text and data will be billed to the author. Proofs should be corrected and returned to and received at the editorial office within 48 hours by express delivery at the author's expense to the address listed above ("Communications").

Offprint Orders. An offprint order form will be sent to the corresponding author with the proofs; if offprints are desired, the form must be returned to the editorial office, preferably with the proofs, but not later than 3 days to avoid late charges. A check for the exact amount in US dollars should be made out to the order of *The Mount Sinai Journal of Medicine*. Please indicate on the check the last name of the first author, and the title of the article. If for one reason or another, the offprint order form is not received with the proofs, it may be obtained directly from the editorial office via telephone or FAX. Offprints are available in minimum quantities of 100, at a cost depending on the number of printed pages and whether covers are desired. The cost of other than routine surface mail delivery, if requested, must be added to the cost of the offprints. Information on the cost of other than routine surface delivery can be obtained from the editorial office.

Required Form for Authors:

AUTHORSHIP RESPONSIBILITY, FINANCIAL DISCLOSURE, AND ASSIGNMENT OF COPYRIGHT

Article Title (type):

Each author must read and sign this form dealing with (1) authorship responsibility, (2) financial disclosure and (3) copyright transfer. An author who was a US federal employee when this work was conducted and prepared for publication, must sign statement (4) instead of statement (3).

1. Authorship Responsibility

I certify that I have participated sufficiently in the conception and design of this work, and the analysis of the data (where applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe that the manuscript represents valid work. I have reviewed the final version of the manuscript and approve it for submission for publication. Neither this manuscript nor one with substantially similar content under my (our) authorship has been published or is being considered for publication elsewhere, except as described in a separate attachment. Furthermore, I agree to produce the original recorded data on which the manuscript is based for examination by the Editor-in-Chief and/or his assignees should such records be requested.

2. Financial Disclosure

I certify that I do not have and have not had an affiliation or financial involvement with or in any organization or entity with a direct financial interest in the subject matter or materials being discussed in the manuscript (eg, employment, consultancies, stock ownership, honoraria), except as disclosed in a separate attachment.

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

3. Copyright

In compliance with the Copyright Revision Act of 1976, the signature of each author on this form shall indicate and be evidence of agreement and mutual understanding with *The Mount Sinai Journal of Medicine*, in consideration of the further action of the *Journal* to review and edit the manuscript being submitted, to transfer, assign, and convey all copyright ownership, including any and all rights incidental thereto, exclusively to *The Mount Sinai Journal of Medicine* if this work is published in the *Journal*.

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

4. US Federal Employees

I was an employee of the US federal government when this work was conducted and prepared for publication; therefore, it is not protected by the Copyright Act and copyright ownership cannot be transferred.

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

Return the original signed form to The Editor, The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, N.Y. 10029. Retain one copy of the form for your file. You may make as many photocopies as needed if your manuscript has more than six authors.

THE
MOUNT SINAI JC
OF MEDICINE

LEVY LIBRARY, MT. SINAI MEDICAL CENTER
3 4805 0497032 9

Forthcoming:

Grand Rounds

Money, Medicine and Methuselah
Christine K. Cassel
The Mount Sinai School of Medicine

Lipostasis and the Control of Body Weight: Cloning of the Obesity (ob) Gene
Jeffrey Friedman
Rockefeller University

The Lactose Permease Meets Frankenstein: New Approaches to Membrane Protein Structure
H. Ronald Kaback
Howard Hughes Medical Institute
University of California, Los Angeles

Silicone Breast Implants and Connective Tissue Disease: An Overview
Harry Spiera and Robert F. Spiera
The Mount Sinai School of Medicine

Theme Issues

Computers in Medicine
Editors: Ray Cornbill and Joseph Kannry

Laparoscopy
Editors: Barry Salky and Michael Edye

Human Immunodeficiency Virus—AIDS
Editor: Henry Sacks

Emergency Medicine
Editors: Andy Jagoda and Lynne Richardson

Reproductive Choice: Genetic Counseling and Assisted Reproductive Technology
Editors: Rosamond Rhodes, Daniel A. Moros, Allyson Robichaud

Available now:

Alumni Theme Issue Part A: Original Articles
Volume 63, Numbers 3&4, 1996
134 pages. $20.00

Cross-Cultural Issues in Psychopharmacology and Alumni Theme Issue Part B
Volume 63, Numbers 5&6, 1996
154 pages. $20.00

THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 64 NUMBER 3 MAY 1997

MAY 14 1997

LEONARD I. MALIS

An Appreciation

Marvin H. Savitz, guest editor

Veterans
Affairs

THE MOUNT SINAI JOURNAL OF MEDICINE

The Mount Sinai Journal of Medicine is published by The Mount Sinai Medical Center of New York and has the following affiliates: Bronx Veterans Affairs Medical Center, New York; Elmhurst Hospital Center, Queens, NY; Queens Hospital Center, Queens, NY.

Editor-in-Chief

Sherman Kupfer, M.D.

Editor Emeritus

Lester R. Tuchman, M.D.

Associate Editors

Harriet S. Gilbert, M.D. Julius Wolf, M.D.

Administrative Assistant

Joseline Ilagan

Assistant Editor for Housestaff

Rochelle Waldman, M.D.
Michael E. Blam, M.D.

Assistant Production Assistant

Mel Meyer

Assistant Editors

David H. Bechhofer, Ph.D.
Constanin A. Bona, M.D., Ph.D.
Edward J. Bottone, Ph.D.
Lewis Burrows, M.D.
Christopher P. Cardozo, M.D.
Mark R. Chassin, M.D., MPH, MPP
Joseph S. Eisenman, Ph.D.
Richard A. Frieden, M.D.
Frederick Friedman, M.D.
Steven Fruchtman, M.D.
Paul L. Gilbert, M.D.
James N. Gladstone, M.D.
James H. Godbold, Ph.D.
Richard S. Haber, M.D.
Noam Harpaz, M.D.
Tomas Heimann, M.D.
Sheldon Jacobson, M.D.
Barry W. Jaffin, M.D.
Joseph L. Kannry, M.D.
Suzanne Carter Kramer, M.Sc.
Mark G. Lebwohl, M.D.
Zvi Lefkowitz, M.D.
Kenneth V. Lieberman, M.D.
Lynda R. Mandell, M.D., Ph.D.
Steven Markowitz, M.D.
Bernard Mehl, D.P.S.
Myron Miller, M.D.
Edward Raab, M.D.
Elliot J. Rayfield, M.D.
Allan Reed, M.D.
Clive Rosendorff, M.D., Ph.D.
Fred Rosner, M.D.
Allan E. Rubenstein, M.D.
David B. Sachar, M.D.
Henry Sacks, M.D.
Ira Sanders, M.D.
Martin H. Savitz, M.D.
Clyde B. Schechter, M.D.
Stuart C. Sealfon, M.D.
Michael Serby, M.D.
Phyllis Shaw, Ph.D.
Alex Stagnaro-Green, M.D.
Barry D. Stimmel, M.D.
Nelson Stone, M.D.
Max Sung, M.D.
Rein Tideiksaar, Ph.D.
Richard P. Wedeen, M.D.
Vincent B. Ziccardi, M.D., D.D.S.

Editorial Board

Barry S. Coller, M.D.
Barry Freedman, M.B.A.
Richard Gorlin, M.D.
Nathan Kase, M.D.
Panayotis G. Katsoyannis, Ph.D.
Charles K. McSherry, M.D.
Jack G. Rabinowitz, M.D.
John W. Rowe, M.D.
Alan L. Schiller, M.D.
Alvin S. Teirstein, M.D.
Rosalyn S. Yalow, Ph.D.

The Mount Sinai Journal of Medicine (ISSN No. 0027-2507; USPS 284-860) is published 6 times a year in January, March, May, September, October, and November in one indexed volume by The Mount Sinai Medical Center, Box 1094, One East 100th Street, New York, NY 10029-6574. Subscription price: individuals (U.S. and Canada), $75 per year; libraries and institutions (U.S. and Canada), $115 per year; individuals (outside U.S. and Canada), $100 per year; libraries and institutions (outside U.S. and Canada), $140 per year. Single copies $20. New subscriptions begin with the first issue of the calendar year. Send notice of change of address 60 days before its effective date. Periodicals postage paid at New York, NY and at additional mailing offices. POSTMASTER: Send address changes to The Mount Sinai Journal of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Telephone number (212) 241-6108; Fax (212) 722-6386. Copyright 1997 The Mount Sinai Hospital.

DISCLAIMER: The statement and opinions expressed in the *Journal* by authors and contributors are solely their own and not those of The Mount Sinai Medical Center or The Mount Sinai Journal of Medicine. All advertisements are expected to conform to ethical standards, and their appearance does not imply endorsement or approval by The Mount Sinai Medical Center and/or The Mount Sinai Journal of Medicine of the products with respect to effectiveness, quality, or safety. The Mount Sinai Medical Center and The Mount Sinai Journal of Medicine do not hold themselves responsible for statements made by the authors or contributors, and for any injury to persons or property which may have resulted from ideas, products, and services referred to in articles or advertisements.

COPYRIGHT: Material printed in the Journal is protected by copyright. In accord with U.S. Copyright law, no part of the Journal may be reproduced, displayed, or transmitted in any form, electronic or mechanical, including photocopying or by any information storage or retrieval system, without prior written permission to do so. Permission should be requested from The Editor. The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574.

THE
MOUNT SINAI JOURNAL
OF MEDICINE

Volume 64
Number 3
May 1997

CONTENTS

Editorial *Martin H. Savitz* 153
The Early History of Neurosurgery in New York *Anton Marti* 155
The Early Days of Microsurgery in Vermont *Julius H. Jacobson II* 160
The Advent of Microsurgery *M. Gazi Yasargil* 164
Leonard I. Malis: An Appreciation *Lawrence Kruger and Aaron J. Berman* 166
Technical Contributions of Leonard I. Malis *Jerry L. Malis* 172
Basic Science Contributions of Leonard I. Malis *Peter W. Carmel* 182
Leonard I. Malis and Prophylactic Antibiotics *Sean I. Savitz* 187
Another Look at Ventriculosubgaleal Shunting Procedures *Martin H. Savitz* 189
Neuroradiology at The Mount Sinai Hospital *Yun Peng Huang* 194
Venous Architecture of Cerebral Hemispheric White Matter and Comments on Pathogenesis of Medullary Venous and Other Cerebral Vascular Malformations *Yun Peng Huang, Toshio Okudera, Akio Fukusumi, Fumiaki Maehara, Aryeh L. Stollman, Roger Mosesson, Mike Lidov, and Harold A. Mitty* 197
Operative Microphotography: A Malis Legacy *Richard J. Radna and Ved P. Sachdev* 207
The Prone-Oblique Surgical Position *Richard J. Radna and Ved P. Sachdev* 213
A Biorbitofrontobasal Interhemispheric Approach for Suprasellar Lesions *Kenji Ohata, Akira Hakuba, Kenji Nagai, Michiharu Morino, and Yoshiyasu Iwa* 217
Microneurosurgery in Suburbia *Martin H. Savitz* 222
Radiologic Evaluation in Patients with Head Injury *Michael H. Brisman and Martin B. Camins* 226

Special Article

John E. Moseley, M.D. 1909–1996 *Jack G. Rabinowitz* 233
Information for Authors 235
Required Form for Authors 237

Statement of Ownership, Management, and Circulation filed with the U.S. Postal Service. Average no. copies each issue for the 12 month period ending December 31, 1996: 15a. net press run, 2805; 15b1. paid and/or requested, 1424; 15b2. paid and/or requested (not mailed), 1424; 15b2. paid and/or requested (mailed), 926; 15c. total paid or requested circulation, 2350; 15d. free distribution by mail, 225; 15e. free distribution by carriers or other means, 80; 15f. total free distribution, 305; 15g. total distribution, 2255; 15h1. copies not distributed (office use, leftovers, spoiled), 150; 15h2. copies not distributed (return from dealers), none; 15i. total number of copies, 2805; percent paid and/or requested, 88.5%. Actual no. of copies of issue published nearest to filing date (November 1996): 15a. net press run, 2000; 15b1. paid and/or requested (not mailed), 1224; 15b2. paid and/or requested (mailed), 433; 15c. total paid or requested circulation, 1657; 15d. free distribution by mail, 243; 15e. free distribution by carriers or other means, 50; 15f. total free distribution, 243; 15g. total distribution, 1900; 15h1. copies not distributed (office use, leftovers, spoiled), 100; 15h2. copies not distributed (return from dealers), none; 15i. total number of copies, 2000; percent paid and/or requested, 83%.

Leonard I. Malis

Editorial

Martin H. Savitz, M.D.

Leonard I. Malis, *Honoris Causa*

Martin H. Savitz began his residency in 1970 when Leonard I. Malis became Professor and Chairman of the Department of Neurosurgery of The Mount Sinai School of Medicine. In 1993, as Chairman of Neurosurgery for the United States Section of the International College of Surgeons, Dr. Savitz presented Chairman Malis with a Lifetime Achievement Award as pioneer, inventor, scholar, educator, and professor of neurosurgery.

Leonard Malis deserves to be honored by The Mount Sinai Hospital as an alumnus, as a basic scientist, as a clinical investigator, as a teacher, and as a world-class neurosurgeon. Thumbing through the pages will acquaint the reader with Dr. Malis's extensive bibliography: contributions to the study of neurophysiology (1–3), creation of a true bipolar coagulator (4), design of a serial cassette changer for cerebral angiography (5), refinement of full-column myelography (6), understanding of spinal stenosis (7, 8), introduction of the binocular microscope into the neurosurgical operating room (9), invention of many instruments key to microneurosurgery (10), and perfection of microsurgical techniques to safely and completely remove tumors of the base of the skull (11), posterior fossa (12), pituitary (13), and spinal cord (14, 15). Colleagues, residents, and students whose academic lives were influenced by the teaching of Leonard Malis have all joined in this tribute to convey even more about the man—his warmth as a mentor, his kindness toward patients in distress, his willingness to treat the financially disadvantaged, and his genuine genius in problem solving.

Among his many awards to date are the Olivecrona Medal of Sweden, the Bordeaux Medal of the City of Bordeaux, the Elsberg Medal of the New York Society of Neurosurgery, the Jacobi Medallion of the Mount Sinai Alumni Association, and the Key to the City of Osaka. Dr. Malis has been an honored guest lecturer at ten medical centers in the United States as well as Switzerland, Mexico, Japan, Sweden, France, Canada, Spain, and Korea. The present Special Issue contains articles by several physicians who personally knew him in each of his various roles. In addition, there are contributions of original clinical research by neurosurgeons who trained under his guidance.

Dr. Malis was blessed with unique talents—ambidexterity and the ability to think of neuroanatomy in three dimensions. Long before the advent of computerized tomography, he could visualize in his mind the shape and dimensions of the spinal canal after looking at AP and lateral planograms of the spine and Pantopaque myelography. He used both hands at the same time; the residents including myself would watch in awe as he simultaneously drew the left and right sides of his patient's axial projection on a blackboard.

Harvey Cushing could only dream of completely removing an acoustic neuroma even with sacrifice of the seventh cranial nerve (16). Dr. Malis studied the neuroradiology and conceived of the positioning of the patient, the operative approach, the instrumentation, and the microsurgical techniques necessary for complete removal of angle tumors (17). Brainstem evoked potentials were introduced at Mount Sinai many years before their availability at other medical centers (18), but Dr. Malis was able to preserve vestibular and cochlear function by sheer mastery of the microanatomy of the posterior fossa. Few neurosurgeons today could manage preservation of hearing or facial nerve function without elaborate intraoperative neurophysiological monitoring. At the height of his career, Leonard Malis alone was operating on 50 acoustic neuromas per year, 1⁄16 of the 800 diagnosed in the United States. Until his last week of surgical practice, patients with angle tumors were flying into New York City from all over the world to be admitted to The Mount Sinai Hospital.

Leonard Malis set the stage for electroneurophysiology, optical enhancement in neurosurgery, and computerized neuro-imaging, which have evolved into minimally invasive endoscopic techniques, positron emission tomography, and magnetic resonance angiography.

References

1. Malis Ll, Pribram KH, Kruger L. Action potentials of motor cortex evoked by peripheral nerve stimulation. J Neurophysiol 1953; 16:161–167.
2. Malis Ll, Kruger L. Multiple response and excitability of cat's visual cortex. J Neurophysiol 1956; 19:172–186.
3. Malis Ll, Loevinger R, Kruger L, Rose JE. Production of laminar lesions in the cerebral cortex by heavy ionizing particles. Science 1957; 1266:302–303.
4. Malis LI. Bipolar coagulation in microsurgery. ln: Peardon RM, Donaghy RM, Yasargil MG, eds. Microvascular surgery. Stuttgart: Georg Thieme Verlag, 1963:126–130.
5. Malis LI. An automatic cassette changer for cerebral angiography. J Mt Sinai Hosp 1957; 24:54–61.
6. Malis LI, Newman C, Wolf BS. Full column technique of lumbar myelography. Radiology 1953; 60:18–28.
7. Epstein JA, Malis Ll. Compression of spinal cord and cauda equina in achondroplastic dwarfs. Neurology 1955; 5:875–881.
8. Wolf BS, Khilnani M, Malis LI. The sagittal diameter of the bony cervical spinal canal and its significance in cervical spondylosis. J Mt Sinai Hosp 1956; 23:283–292.
9. Malis LI. Hemostasis in neurosurgery. In: Yasargil MG, ed. Microsurgery applied to neurosurgery. Stuttgart: Georg Thieme Verlay; 1969:41–47.
10. Malis LI. Instrumentation and techniques in microsurgery. Clin Neurosurg 1979; 28:626–636.
11. Decker RE, Malis Ll. Surgical approaches to midline lesions at the base of the skull: a review. J Mt Sinai Hosp 1970; 37:417–420.
12. Malis LI. Microsurgical treatment of acoustic neuromas. In: Hands H, ed. Microsurgery. Tokyo: Igako-Shoin Ltd; 1975:105–120.
13. Malis LI. Tumors of the parasellar region. In: Thompson RA, Green JR, eds. Advances in neurology. New York: Raven Press; 1976:281–299.
14. Malis Ll. Intramedullary spinal cord tumors. Clin Neurosurg 1978; 25:512–539.
15. Malis LI. Microsurgery for spinal cord arteriovenous malformations. Clin Neurosurg 1979; 26:543–555.
16. Cushing H. The surgical mortality percentages pertaining to a series of two thousand verified intracranial tumors. Arch Neurol Psychiatry 1932; 27:1273–1280.
17. Malis Ll. Acoustic tumor. In: Pillsbury HC, Goldsmith MM, eds. Operative challenges in otolaryngology/head and neck surgery. New York: Yearbook Publishers; 1989:77–91.
18. Fridmann J, Zappulla RA, Bergelson M, et al. Application of phase spectral analysis for brain stem evoked potential detection in normal subjects and patients with posterior fossa tumors. Audiology 1983; 22:99–113.

The Early History of Neurosurgery in New York

Anton Marti, M.D.

Editor's Note: Cerebral angiography, introduced by Egas Moniz in 1927, initially was beset by complications caused by primitive contrast media such as sodium bromide, sodium iodide, and radioactive thorium dioxide. Dr. Gross experimented with diodrast, an iodide compound usually used for myelography and intravenous pyelography. When he was ready to demonstrate the technique at the Neurological Institute, the professors assembled and watched as he deftly exposed the carotid artery, injected a 70% diodrast solution, and changed the x-ray cassette once by hand to produce an arterial phase and a venous phase. As the senior staff reviewed the films, Dr. Gross was treating the patient for grand mal convulsions and heard the communal advice: "Very nice, Sidney, but just don't ever do it again!" Reducing the concentration of diodrast to 50% or 35% allowed carotid angiography to continue as an essential neuroradiologic study (1).

Introduction by Dr. Marti

Dr. Gross would occasionally refer to his parents' Hungarian background, but he was born in 1904 and raised in Cleveland where he obtained his degree from Western Reserve in 1928. He interned at the Michael Reese Hospital from 1928 to 1929 and was a resident from 1929 to 1931 at the Neurological Institute where Dr. Charles Elsberg was chief of neurosurgery. Dr. Elsberg had been one of the three chiefs of general surgery at The Mount Sinai Hospital and had gradually increased his neurosurgical specialization. When Dr. Elsberg left for the Neurological Institute, Dr. Ira Cohen became the first Chief of Neurosurgery. After training in neurology at The Mount Sinai Hospital with Dr. Israel Wechsler, Dr. Malis became Dr. Cohen's resident in neurosurgery and then took a fellowship year in neurophysiology with Dr. John Fulton at Yale University. When Dr. Malis returned to Mount Sinai in 1951 as an Assistant Attending, Dr. Cohen had retired and Dr. Leo Davidoff was head of the Department of Neurosurgery. Dr. Gross became Chief of Neurosurgery in 1957, and Dr. Malis was appointed as an Associate Attending Neurosurgeon (2).

Dr. Gross frequently mentioned his fellowship under Dr. Ernest Sachs (3) at Washington University in St. Louis from 1931 to 1933. During the same period, he studied neuropathology with Dr. Percival Bailey at the University of Chicago. There was a natural inclination to emphasize neurosurgical bloodlines, the closer to Harvey Cushing the better. In addition to having trained directly under Cushing, Dr. Sachs had previously spent time with Sir Victor Horsley in England, and Dr. Bailey had visited with Professor Pierre Marie in France.

Dr. Gross referred frequently to the controversy that raged for more than 50 years over the attribution of credit for ether anesthesia. Dr. William T. G. Morton, a dentist in Connecticut, was dissatisfied with nitrous oxide and asked Charles Jackson, a Boston chemist, for another possible agent. Ether was first used for anesthesia by Dr. Morton in 1846. This seemingly marginal issue may have been on Dr. Gross's mind because he himself administered ether anesthesia many times for neurosurgical procedures. In ad-

---

With a previously unpublished manuscript by Sidney W. Gross, M.D.

Address reprint requests to Anton Marti, M.D., Veterans Administration Medical Center, 30 W. Kingsbridge Avenue, Bronx, NY 10468.

dition, John F. Fulton's biography of Harvey Cushing, which was often quoted by Dr. Gross, records that Dr. Cushing traveled by train from Baltimore to Boston in 1908 with the famed pathologist, Dr. William H. Welch. Dr. Welch was invited to give the Ether Day Address at the Massachusetts General Hospital to commemorate the introduction of surgical anesthesia and kept Dr. Cushing amused because the address was written entirely on the trip north. Many a resident and assistant surgeon were cajoled by Dr. Gross: "Don't stand there like a Buddha!" The expression, ". . . sitting like a Buddha," is also attributed to Dr. Cushing, who came to Mount Sinai in 1931 to deliver the William H. Welch Lecture on pituitary-hypothalamic effects on the stomach.

When I was accepted into training by Dr. Gross, the Neurosurgery Service included three residents at The Mount Sinai Hospital and one resident at Elmhurst Hospital in Queens. The residents performed all the neuroradiologic procedures including myelography with Pantopaque. Pneumoencephalography was accomplished with an "improved" chair which had the patient spinning like a ferris wheel after spinal injection of air. Direct puncture of the carotid, brachial, or vertebral artery was followed by injection of contrast media and the loud banging of Dr. Malis's automatic multiple cassette changer which made serial angiography possible. Because of differing personalities, backgrounds, and professional interests, the three attending neurosurgeons brought a wealth of concepts and operative approaches to the residency program. Dr. Gross drew from tried-and-true traditional methods. Dr. Malis brought consistent innovation to neurosurgical technique. Dr. Bruce Ralston never performed any operation the same way twice.

In those days, the sanctity of Friday grand rounds included meeting in the Board of Trustees Room with its elegant hardwood table and chairs, followed by lunch in the hospital cafeteria which offered hot meals and hand-carved corn beef sandwiches, before the neuroradiology conference led by Dr. Yun Peng Huang. Dr. Gross would always finish the work week with fine cigars, which he provided to the residents. Dr. Malis smoked a pipe, and Dr. Ralston was never without his cigarillos . . Most people can remember what they were doing at the time of President Kennedy's assassination. The Neurosurgery Service was assembled in the old x-ray area peering at angiograms spread over the many view boxes when the terrible news from Dallas permeated the cigar smoke.

Christmas parties at Dr. Gross's upper East Side townhouse office were sometimes alternated with cookouts at his house in Hewlett Harbor. In later years, the annual departmental gatherings were held at the Plaza Hotel. On some of the nights that he spent in town, Dr. Gross would invite the resident-on-call out to supper. There were three choices and exactly three restaurants to match—Oscar's for seafood, Lisa Chang's Palace for Chinese, and Murphy's on Second Avenue for steaks.

I have always associated Dr. Gross with the institution of marriage. During my training at The Mount Sinai Hospital, he hosted the wedding of one of my fellow residents at his townhouse. In 1966 when Dr. Gross had become a widower, the sweetheart from his medical school days reentered his life. In October, I was invited to attend a national neurosurgical meeting in San Francisco. During the flight, Dr. Gross told me that they were on their honeymoon. All three of us toured the Monterey peninsula. Some months later, Dr. Gross arranged a position for me in Barcelona with Professor Adolfo Ley, one of the pioneers in neurosurgery in Spain. Dr. Ley had been in training with Dr. Gross in Chicago under Dr. Bailey. Even more interesting is the fact that Dr. Gross stood in as proxy for the bride during Dr. Ley's wedding so that Mrs. Ley, then in Spain, could get a visa and join her husband in the United States.

During 1994, when many of us became aware of Dr. Gross's failing health, many colleagues and former residents traveled to Santa Monica for a final visit. Raphael Quinonez, Michael Sukoff, and other transplants from Mount Sinai to the West Coast kept a closer watch, but all were present in spirit when Dr. Gross's ashes were sprinkled over the Pacific Ocean in 1995. The life of Sidney W. Gross spanned the entire era from the beginnings of the specialty practiced by Harvey Cushing to the technological advancements of microscopic technique, which turned neurosurgery from a "premortem examination" into a curative intervention.

The Following is an Unpublished Manuscript Read by Dr. Gross at the Neurological Institute in 1972

Neurosurgery in New York City in the early days was intimately connected with the Neurological Institute, which was dependent on the support of the first specialists in neurology. The development of neurosurgery as a specialty was the result of the advancements in general surgery and anesthesia which made feasible exploration of all body cavities including the cranium and vertebral column. The principles of antisepsis and aseptic technique proposed by Lister and Semmelweis were well known.

At first, neurology, as a specialty, was an offshoot of internal medicine. Pierre Broca, a graduate of the University of Paris, who began his career in pathology, demonstrated before the French Anthropological Society in 1861 that a patient who suffered aphasia in life had a lesion in the left frontal lobe at autopsy. From this and subsequent observations, Broca concluded that the left third frontal convolution was essential to articulated speech. Broca's area dominated research in cerebral localization until 1870, when Fritsch and Hitzig in Germany stimulated the cerebral cortex electrically and began the field of neurophysiology by confirming the prediction of Hughlins Jackson from his own studies of focal epilepsy.

Among the earliest neurologists in the United States was S. Warren Mitchell in Philadelphia, whereas William Hammond, Frederick Peterson, and Bernard Sachs were in New York City. Bernard Sachs was the uncle of Ernest Sachs, and his relationship with Harvey Cushing played a major role in his nephew being accepted into training in Boston. Charles L. Dana was another early pioneer and still on the staff when I arrived in 1929. Unfortunately, he was suffering from senile dementia and kept prescribing mercury and large doses of sodium iodide which had been in use decades earlier. In a letter to his wife in 1900, Harvey Cushing mentions his disappointment with Dana's presentation at a meeting in Philadelphia.

The New York Neurological Society was organized in 1874. A year later, Dr. Hammond, Professor of Neurology at Bellevue Hospital, one of the prime movers of the group, founded the American Neurological Society. Dr. Hammond was author of one of the earliest treatises on diseases of the nervous system published in the United States. He had been a general in the Union Army during the Civil War and attained some notoriety by being court martialled and acquitted. Harvey Cushing spoke to the New York Neurological Society in 1909 at the New York Academy of Medicine on the topic, "Some Aspects of Pathological Physiology of Intracranial Tumors."

Nearly all of the early leaders in neurology in New York City were trained at the Vanderbilt Clinic and joined in the effort to found the Neurological Institute. Joseph Collins deserves the credit for establishing the Neurological Institute. Along with Percival Bailey and Frederick Peterson, he assembled a group of friends and prominent businessmen to discuss founding a hospital devoted to the diagnosis and treatment of neurological diseases. In 1909, Charles Elsberg was invited to join the group because he was one of the first general surgeons to perform operations on the spine and brain exclusively. It was a long time before many of the general surgeons in New York were willing to refer patients to specialists. Even in 1934, when I came back to New York City after completing my training in St. Louis and Chicago, many surgeons would give ward cases to younger colleagues who were trying to specialize, but they still performed laminectomies and craniotomies on their private patients with spine fractures and brain tumors.

Some of the earliest neurosurgical procedures were directed toward the relief of the excruciating pain of trigeminal neuralgia. In 1858, J. M. Carnochan, Professor of Surgery at New York Medical College, developed an approach through the maxillary sinus to reach the second division of the fifth cranial nerve. G.R. Fowler carried out various peripheral neurectomies for tic douloureux. R. Abbe of St. Luke's Hospital exposed branches of the trigeminal nerve intracranially and interposed pieces of gutta percha between the cut ends to prevent regeneration. By 1891, Frank Hartley had practiced dividing the branches intracranially on cadavers for more than a year before operating with an incision at the base of the zygoma and a groove in the temporal bone made with a chisel. The bone was lifted with a periosteal elevator and the middle meningeal artery was tied off before separating the dura and exposing the foramina rotundum and ovale. The cut ends of the nerve were pushed into the foramina to interfere with regeneration. Fedor Krause devised a similar operation in Germany and published his findings in 1892 (4). Controversy arose over who was the originator because Hartley's article was published in The New York Medical Journal in 1892. I was fond of simpler neurectomies and percutaneous blocks because many private patients would not consent to more invasive procedures.

Charles Elsberg studied with Mikulicz in Germany. Dr. Elsberg was a shy man but came to know me well and often spoke about his experiences in Europe. While still performing some general surgery, he published his first paper in 1904 on two cases of cerebellopontine angle tumor. By 1910, Dr. Elsberg was applying himself more and more to neurosurgery. Several of his associates did not maintain their specialization in neurological surgery because they could not make a living.

Edmund Beer became a urologist, Harold Neuhof specialized in thoracic surgery, and James Kenyon began to stay home and tinker with his motor boat while his wife was a successful general practitioner. Dr. Elsberg was a pioneer in surgery of the spinal cord and became an internationally recognized authority. Patients came from all over the United States, and other doctors visited to learn his techniques. Advancements in cranial surgery kept apace. Dr. Elsberg attempted to relieve certain types of increased intracranial pressure by puncturing the corpus callosum and was still performing the operation when I arrived in 1929.

No history of neurological surgery in New York City would be complete without mentioning two grand ladies. Miss Revington, the Superintendant of the Neurological Institute from 1914 until her retirement, was very active when I was there. Miss Dwyer was the Chief of Nursing. Both ladies remained single and willingly took the role of foster mother to all the residents. We were well fed and comfortable with our family away from home.

Before my arrival in 1929, there were many stories about what took place at East 67th Street. In those days, the Neurological Institute was next to a police station. There were several incidents, some quite shocking, involving felons and prostitutes. As the reputation of the Neurological Institute increased, the outpatient department became overwhelmed and the waiting list for admission to the ward was lengthy. In 1911, a total of 89 major surgical procedures were performed. By 1916, 128 were performed, and the Neurological Institute was further stressed by many patients from a polio epidemic.

Immediately before the United States entered World War I, several Canadian soldiers with wounds of the nervous system were admitted. During the war, the staff was greatly reduced because members entered military service. Dr. Zabrisky was always affectionately referred to as "the Colonel." Dr. Elsberg provided neurosurgical training for more than 200 medical officers. About this time, Dr. Stookey gave up his interest in orthopedics and became a neurosurgeon at the Neurological Institute.

In 1918, Dr. Cushing tried to establish a National Neurological Institute but there was stiff resistance over the name from the New York contingent. In 1919, Joseph Collins, Percival Bailey, and Frederick Peterson resigned from the active staff. All three had been such prime movers at the hospital, but left in a huff over some sort of internal fracas. Drs. Zabrisky, Foster Kennedy, and Timmy, whose great interest was endocrinology, became the leading lights. At the meeting of the American College of Surgeons in New York in 1919, Dr. W. J. Mayo declared: "A new surgical specialty of neurological surgery has been founded." The Society of Neurological Surgeons was founded in 1920 by Harvey Cushing at a meeting in Boston. The original ten members included A.W. Adson, Charles Bagley, Charles Dowman, Charles Elsberg, Charles Frazier, Samuel Harvey, Gilbert Horrax, Dean Lewis, and Ernest Sachs. Additional founding members were Edward Archibald, Claude Coleman, George Heuer, Allen Kanavel, W. Jason Mixter, Howard Naffziger, and Alfred Taylor. Walter Dandy was asked to join but refused the invitation. The "Senior Society" was superseded by the more inclusive Harvey Cushing Society in 1932.

In 1921, the first clinic for fourth year medical students from Columbia College of Physicians and Surgeons was held at the Neurological Institute. By 1926, the number of major surgical procedures had increased steadily to 223. The site for the new building was chosen about then. When I arrived in 1929, the staff consisted of Drs. Elsberg, Taylor, Kenyon, Stookey, Davidoff, and Masin. Residents from neurology rotated through the neurosurgical service for four to six months, but they seemed to spend most of their time arguing over the findings on neurological examinations. The young attendings, Drs. Davidoff and Masin, were first assistants; and the residents on service were second assistants. Anesthesia in those days was by the drop ether method, and I spent many hours under the drapes pouring ether over the patient's mask for Dr. Elsberg or Dr. Stookey.

After the Neurological Institute moved to Washington Heights, there were many distinguished visitors from all over the world. Dr. de Martel brought his craniotome with him and was allowed to scrub in with Dr. Elsberg. The instrument was finally donated to the Bronx Veterans Administration Medical Center, which became one of the affiliated hospitals of the Columbia College of Physicians and Surgeons. Unable to face the defeat of France, Dr. de Martel committed suicide when the Germans occupied Paris in 1940. The craniotome was lost, but a set of retractors, designed and donated by Dr. Taylor (5) as a precursor of microdiscectomy, remained at the Bronx VA Hospital. Nurse Louella Carter, who was trained at the Peter Bent Brigham Hospital in Boston, was the operating room supervisor at the Neurological Institute. There were legendary feuds between Dr. Elsberg and Dr. Stookey, and I was asked by the more timid Dr. Elsberg to be an intermediary. One day, Dr. Stookey came into the operating room without a mask. Dr. Elsberg was fuming but kept silent until the end of the case when he told me to inform Dr. Stookey that his deviation from aseptic technique was unacceptable.

The provision of laboratory space was delayed. There was a small, dark cubbyhole in the basement where we performed post mortem examinations. The only photography was made possible with a plate camera to record illustrations for the Bulletin of the Neurological Institute. Samuel Orten was then appointed head of the Department of Neuropathology with a laboratory in the Columbia College of Physicians and Surgeons. Abner Wolf, who had worked with Jakob at the Brain Institute in Germany, joined the new department but had to learn how to remove a brain from the skull because he had previously enjoyed the help of a mortuary technician.

Of course, neuroradiology was in its infancy. C. W. Schwartz was head of the Department of Radiology but most of the imaging of the brain and spine was performed by Cornelius Dyke (6), who had worked with Merrill Sosman at the Peter Bent Brigham Hospital in Boston and gained access to Harvey Cushing's teaching files. Pneumoencephalography was available, but Dr. Elsberg was unwilling to perform a study with the potential complications of coma and death (7) until Drs. Dyke and Davidoff demonstrated that they could inject air into the ventricles with little morbidity and no mortality. Most diagnoses of intracranial neoplasm were based on clinical findings, and almost all brain operations were exploratory.

Dr. Stookey had many patients at other New York City hospitals, especially at the Post Graduate Hospital where Ed Scarff eventually joined him. William Sharpe and his brother Norman worked at the Broad Street Hospital and together wrote a textbook on brain surgery (8). The largest number of procedures were performed on mentally retarded patients, and the operations were later found to be totally ineffective. Another neurosurgeon was Wilford May who developed an operation for epilepsy, which consisted of creating an osteoplastic flap over the sagittal sinus and inserting a metal plate.

Bronson Ray, who became Chairman of Neurosurgery at Cornell, and J. Lawrence Pool, who became Chairman at the Neurological Institute, were interviewed by Byron Stookey and Max Peet at the earliest board examinations. Both candidates were witnesses to heated arguments which took place between the examiners over differing surgical techniques. Every question led to such lengthy disagreement that there was little time for either examinee to demonstrate his knowledge.

Dr. Elsberg continued in active practice until 1936 when he retired at the age of 66. He married Jane Stewart who had been working in one of the laboratories and settled down to the life of a country gentleman until his death in 1948. Byron Stookey became the new chief, and the history of neurosurgery in New York City is well recorded since then.

References

1. Gross SW. Cerebral angiography by means of a rapidly excreted organic iodide. Arch Neurol Psychiatry 1940; 44:217–222.
2. Berman AJ. Leonard I. Malis. Surg Neurol 1985; 23:464–467.
3. Gross SW, Sachs E. Spina bifida and cranium bifida: a study of 103 cases. Arch Surg 1934; 28:874–888.
4. Krausse F. Resection des Trigeminus, Innerhalb der Schadelhole. Verhandl d Deutsch Geselsch f Chir 1892; 21:199–210.
5. Taylor AS. Unilateral laminectomy. Ann Surg 1910; 51: 529–533.
6. Dyke CC, Gross SW. The roentgenography of pituitary tumors. Bull Neurol Inst NY 1931; 1:211–228.
7. Riggs HW. The dangers and the mortality of ventriculography. Bull Neurol Inst NY 1934; 3:210–231.
8. Sharpe W, Sharpe N. Neurosurgery: principles, diagnosis, and treatment. Philadelphia: JB Lippincott; 1928.

The Early Days of Microsurgery in Vermont

JULIUS H. JACOBSON II, M.D.

Editor's Note: Dr. Jacobson became Director of the Vascular Surgical Service in 1962 and was instrumental in establishing a hyperbaric chamber at The Mount Sinai Hospital for the treatment of myocardial infarction and cerebrovascular accidents. Greater than normal atmospheric pressure was made possible within a chamber, 45 feet long and 12 feet in diameter, which functioned both as a treatment center and an operating room. The proposed clinical research hypothesized that hyperbaric oxygenation would provide protection to patients before and during microsurgery for cardiovascular or cerebrovascular occlusion. More than 1,700 operations were performed, primarily for aortic aneurysm repair and carotid endarterectomy.

IT IS A PRIVILEGE TO PARTICIPATE in this special issue of the *Mount Sinai Journal of Medicine* that honors Leonard Malis. I have often thought that if I had the riches of Croesus to contribute to advances in medicine, I would establish a foundation to enable bright young people bound for medical training to get a Ph.D. as well in some unrelated field, such as Art History or Ceramic Engineering. With the intellectual cross-fertilization that would result, some of them might then approach Leonard's intellectual breadth. He combines humanism with medical training, mechanical and electronic knowledge, and the practical ability to go into his home shop where, with his lathe, band saw, and milling machine, he can transform an idea into a device. The combination of his superlative skills in neurologic and neuroradiologic diagnosis and his neurosurgical operating ability, which is virtually unequaled, with this remarkable background resulted in his most remarkable achievements in surgery to solve the most difficult and challenging problems. Little wonder that his neurosurgical leadership mandates this volume.

After serving in the US Navy in World War II, I completed college and received a master's degree in Cell Physiology. This interlude, before medical school and a 7-year surgical residency, was important because the use of a microscope became second nature. Within a year of completing my training at Presbyterian Hospital in New York City, I moved to the University of Vermont in 1960 as Associate Professor and Director of Surgical Research. The Department of Pharmacology asked me to cooperate in a study that involved denervation of the canine carotid artery. It became clear that the only sure way to achieve this was to divide and reanastomose the artery. Considering the state of the surgical art at that time, arteries less than 6 mm could not be anastomosed successfully. It became obvious, as I set out to challenge this presumption, that the problem was the eye not being able to see well enough to guide the hand properly. Thus, a small error in suture placement which was readily tolerated in the human aorta would spell failure in the 3-mm canine carotid. Experimentation to improve vision was begun by using the magnifying spectacles then available, jeweler's loupes, or large magnifying glasses placed over the operative area. Suddenly the epiphany occurred. I remembered wandering into an ear, nose, and throat

---

Address reprint requests to Julius H. Jacobson II, M.D., Box 1273, The Mount Sinai Hospital, One Gustave Levy Place, New York, NY 10029.

(ENT) operating room at Presbyterian Hospital and peering through the microscope during a stapes mobilization (1).

I immediately went to the Mary Fletcher Hospital to borrow an operating microscope. The resistance to moving an expensive piece of equipment and contaminating it in the animal laboratory was monumental, even as it might be today. However, that same day we did the first canine carotid anastomosis with the microscope. I shall never forget how appalled I was by all the loose fibers sticking out of the surgical sponges. From then on the anastomoses were successful, but the instruments were crude, the sutures and needles were too large, the operating field was neither stable nor controllable, all of us had some degree of tremor, and the first assistant could not see to be of help.

The local jewelry store solved the forceps problem. I still go to the jewelry districts in New York City to buy forceps at one-twentieth the cost of a surgical supplier. The problem of the tremor resulting from the party the night before was resolved when I remembered the use of the lathe rest in a machine shop course I had once taken. We all soon learned to rest the instruments on a stable part of the operative field. Along these same lines, one needed fine finger motion to control the needle holder and scissors rather than the wrist motion imparted by holding the ring handles. Spring-handled instruments had been developed for use in eye and ear surgery and simply had to be modified for our deeper operations. I treasure the memory of meeting with Dr. Castroviejo, a pioneering eye surgeon, who showed me a felt-lined card holding 17 such instruments, each with a different lock mechanism (to this day a maintenance problem). The instability of vessel clamps was easily resolved by placing them in holding clamps attached to the operating table and providing a screw adjustment to control the position of the vessel ends. The V. Mueller and Storz companies quickly made suitable lines of instruments available.

Willis Potts was a pediatric surgeon in Chicago who had devised and perfected one of the early "blue baby" operations. He developed a surgical clamp with a single row of fine teeth along each of its jaws. The two arteries that were to be anastamosed could be clamped atraumatically. An instrument maker named Richter secured permission from Dr. Potts to patent the design. During the Korean Conflict, the United States Army ordered two of these clamps for every base hospital in the world. Richter, a perfectionist, could not keep up with the orders but never licensed the design to others. Patents and royalties have feathered many a nest egg.

Before our work, the sutures available were no finer than no. 6-0, by USP standard. Ethicon came to the rescue with a suture 1/1,000 and a swaged needle 5/1000 of an inch in diameter. The needle required a skilled craftsman to drill the hole in the needle stock. That year, 1960, a Miniaturization Awards Committee was established by the industry. We received the runner-up award for the needle-suture combination. The first prize went to the Bulova Watch Company for developing a tiny gear with 360 teeth that was used in their Accutron watch. The physics were such that if the gear had been any larger, there would be no metal strong enough to withstand the pressures involved. Leonard Malis had no trouble understanding the physical principle involved, but I still do.

The final major difficulty was securing a microscope that would allow the surgeon and the assistant to see the operative area simultaneously, at the same or at different levels of magnification. I went to the American Optical Company and to Bausch & Lomb. As is often the case, middle management was cooperative but top management said "no" when they couldn't immediately envision a large market. The Carl Zeiss company was different and sent over the engineer who had developed the original single binocular operating microscope. He observed what we were able to do, and without further consultation, agreed to build one (and only one) of the desired double binocular microscopes, later named the Diploscope. I subsequently learned that this distinctive company culture emanated from decisions made when the company was formed. Zeiss and his technician, Abbe (of condenser fame), had agreed that half of all profits would be plowed back into research and development. Zeiss asked me to go over to Oberkochen, Germany to evaluate the prototype model in the event that changes had to be made before shipment. (This first microscope is now going to the Smithsonian Museum in Washington, DC.) Why was their plant in Oberkochen, a small city that is difficult to get to? After World War II, the American government wanted to reconstitute the company in the allied occupation zone. The previous site had been at Jena in the Russian zone, which was to become East Germany. Our occupation forces lined up a nucleus of 150 Zeiss personnel to set up the new factory. The tale goes that the decision for Oberkochen was made by an American officer closing his eyes and sticking a pin in a map of the future West Germany.

The microscope arrived, the instruments and suture materials seemed to be fine, and I had cage space in the laboratory for 160 dogs. (This would be out of the question financially for a single laboratory today.) The next year was the most productive of my life. Eighteen papers were published. Just about every small tubular structure in the body was attacked, singly and often in combination: arteries (with particular attention to the coronary arteries), veins, lymphatics, nerves, ureters, vas deferens, and Fallopian tubes. Limbs and digits were reimplanted. The rat was used for organ transplantation experiments. Today, the rat models of kidney and heart transplants are a keystone in the evaluation of antirejection drugs for organ transplantation. Sometimes advances in one field supersede those in others. The perfect example of this is Fallopian tube reconstruction which was widely and successfully practiced until the technique of *in vitro* fertilization did away with the need for it.

Our first paper on the technique was presented at the Surgical Forum of the American College of Surgeons; accolades were received and national publicity resulted. Nevertheless, I shall never forget how Dr. Al Humphries, Chief of Vascular Surgery at the Cleveland Clinic, stood up to discuss the paper and, after words of faint praise, said that he was sure Dr. Jacobson realized that the technique was fine for experimental work but that it would be completely impractical to use a microscope in the clinical operating room. It is said that people welcome new ideas but reject new experiences. I have observed that this is generational; predictably, the young are eager, the older drag their feet. The laparoscopic surgical revolution seems to bear this out. Whatever the case, so many visiting surgeons came to Burlington, Vermont that we set up a permanent operating table at which there was a single binocular microscope because the only Diploscope was needed for the frenetic experimental work. The improvements that took place allowed us to successfully reconstruct vessels down to a 1.0-mm diameter. Thirty-five years later the practical level has been reduced to 0.5 mm.

One of the earliest visitors was Dr. Donald Effler, Chief of Thoracic Surgery at the Cleveland Clinic. He came to spend a week. At that point, Dr. Mason Sones at their clinic had worked out the method of performing coronary arteriography. Eighteen cases of coronary revascularization had been performed (none of them were the coronary artery bypass graft of today), but it was obvious that better technical performance was needed. Dr. Ernesto Suarez, my research fellow and coauthor of our first paper (2), went to the Cleveland Clinic for a fellowship on Dr. Effler's service and helped to begin the specialty that coronary bypass surgery is today.

Staying with coronary revascularization but moving ahead in time to the Mount Sinai period,. . . Dr. George Green, a cardiac surgeon from St. Luke's Hospital in New York City, learned the technique with the idea of anastomosing the internal mammary artery to the coronary. Everyone agreed that the internal mammary had better patency and longevity than the more commonly used saphenous vein. Unfortunately, there are only two internal mammary arteries; and they cannot be tailored and swung around as the saphenous veins can.

Clinically, cases of stroke caused by middle cerebral emboli seemed made to order for applying the new methodology. I sought the aid of Dr. R.M.P. Donaghy who was Chief of Neurosurgery at the University of Vermont. One could never find a better collaborator (3). We performed four operations with mixed results, but in 1961 I was invited to present the paper at the Harvey Cushing Society meeting in Mexico City. My main goal after being appointed Director of Vascular Surgery at The Mount Sinai Hospital in 1962 was to apply microsurgical techniques directly to occluded arteries in the heart and brain, but I never accomplished the mission.

One day in 1965, a young Turkish neurosurgeon, M. Gazi Yasargil, appeared at Mount Sinai. He turned out to be the hardest working man whom I have ever encountered. You may recall that Sir William Osler stated that the magic word of medicine was work which "makes the dull student bright, the bright student brilliant, and the brilliant student steady." By that definition, Leonard Malis and M. Gazi Yasargil are "steady." Within a very short time it was obvious that I had nothing more to teach Gazi. Therefore, I sent him up to work with Dr. Donaghy, my former collaborator at the University of Vermont. Under any circumstance, the history of neurosurgery underwent a sea change; an estimated one half of all neurosurgical procedures are now being carried out with the aid of a microscope. Later, Gazi was kind enough to put my name on a paper (4) that I asked him to present at the Society of University Surgeons on temporo-middle cerebral bypass, an operation that has been discounted because of lack of efficacy in a controlled study. In my opinion the study was flawed; someone should again take up a cudgel for temporo-middle cerebral bypass along with middle cerebral thrombendarterectomy. I believe that both operations have merit and that the proof awaits more rigorous patient selection.

At the University of Vermont in 1966, Donaghy, with the help of Yasargil, presented the first course in Microsurgery. Leonard Malis, who had been using a dissecting microscope in his animal laboratory since 1952 and who had conducted his first clinical case, using a borrowed ENT microscope in 1965, was an invited speaker. He spoke on hemostasis with bipolar coagulation in microsurgery. By 1967, Leonard had changed his clinical practice to do only microsurgical procedures and had carried out his first superficial temporal artery-middle cerebral artery bypass, achieving an excellent result. By 1968, Leonard had established a yearly microneurosurgical course at Mount Sinai. He went on, with his extraordinary innovative and engineering talent, to create a state-of-the-art neuromicrosurgical operating room and a host of instruments to use in it. Among these were the Malis cautery which has proved to be a milestone in controlled cauterization, allowing precision of application but avoiding damage to immediately surrounding tissue. I can remember sitting in his hospital office while we watched the microscopic field in an operation being performed floors away. The television monitor was also equipped with two-way voice communication so that suggestion and direction could be given to the operating surgeon. Later, I became editor of the journal *Microsurgery* and, because of the number of neurosurgical submissions, asked Leonard to become coeditor, which he did with his usual distinction.

Microsurgical methodology is now utilized in all the surgical specialties. The future will be replete with operations that we cannot even conceive of today. In the specialty of vascular surgery there is no doubt in my mind that one day the operation that I most dislike doing, amputation, will often be followed by transplantation of cadaver limbs. I am also certain that the qualities that have made Leonard Malis so great a neurosurgeon will lead to his continued contributions in his retirement.

References

1. Holmgren G. Some experiences in the surgery of otosclerosis. Acta Otolaryngol 1923; 5:460–465.
2. Jacobson JH, Suarez EL. Microsurgery in anastamosis of small vessels. Surg Forum 1960; 2:243–247.
3. Jacobson JH, Wallman LJ, Schumaker GA, et al. Microsurgery as an aid to middle cerebral artery endarterectomy. J Neurosurg 1962; 19:108–114.
4. Yasargil MG, Krayenbuhl H, Jacobson JH. Microneurosurgical arterial reconstruction. Surgery 1970; 67:221–228.

The Advent of Microsurgery

M. Gazi Yasargil, M.D.

Editor's Note: Prof. M. Gazi Yasargil began his neurosurgical training at University Hospital, Zurich, Switzerland with Professor Hugo Krayenbuhl in 1953. He was appointed to the position of chairman of the neurosurgical department in Zurich in 1973, where he remained until his retirement in January 1993. Since October 1994 he has been Professor of Neurosurgery at the University of Arkansas College of Medicine, Little Rock.

My relationship with Drs. L. Malis, J. H. Jacobson, and Yun Peng Huang played a very special role in the development of microsurgical techniques and their application in numerous surgical disciplines.

In the early 1960s, open heart surgery was occasionally followed by cerebral arterial embolization, particularly when extracorporeal circulation equipment was used. The question arose as to whether the emboli which occluded cerebral arteries of 1.0 to 2.0 mm in diameter could be removed and the artery repaired using microsurgical techniques. In 1962, a publication by Jacobson et al. (1) directed our attention toward the research laboratory at University Hospital in Burlington, Vermont. In 1960, Dr. J. H. Jacobson, together with his assistant Dr. E. L. Suarez, began to use the operating microscope for microvascular procedures on small vessels. On August 4, 1960, with Dr. R. M. P. Donaghy, a neurosurgeon, they performed an endarterectomy of the occluded middle cerebral artery in a patient, who was later described in the 1962 publication. After this publication, I contacted Dr. Donaghy and proposed that I come to his laboratory in the fall of 1965 to learn the skills of the microtechniques developed by him and his operating nurse, Mrs. J. Roberts. Dr. Jacobson had already left Burlington to become chief of vascular surgery at The Mount Sinai Hospital, New York.

Within 6 months after joining Dr. Donaghy, I was able to perform successfully all types of reconstructive surgery on small vessels in the extremities of rats and rabbits. However, my attempt to apply these microtechniques to reconstruct brain arteries in the dog was unsuccessful. The problem was mainly caused by difficulty in obtaining the necessary and precise hemostasis in the surgical field using the available Bovie coagulator. Budget limitations did not allow the laboratory to buy a new coagulator for $500; instead, a small reconditioned unit was purchased for $150. It turned out that this bipolar unit was very effective. The quality of the bipolar coagulator was immediately evident, because it provided point coagulation and thereby controlled hemostasis in an artery or vein without any adverse effect on the vessel wall and adjacent structures. This result was greatly appreciated, because instant and effective hemostasis during microvascular procedures on brain arteries in the dog allowed the surgeon to continuously maintain a clean and clear surgical field. The bipolar coagulator had been developed and used in the laboratory by Dr. L. Malis for many years, but its technical aspects were not mentioned in any publication until recently. The combination of microvascular techniques with the use of precise bipolar coagulation technique turned out to be a real surgical advance and opened a new surgical era, not only for neurosurgery but also for all microsurgical disciplines.

In the summer of 1966, I traveled to several

Address reprint requests to Professor M. Gazi Yasargil, Department of Neurosurgery, University of Arkansas College of Medicine, 4301 West Markham, Slot 507, Little Rock, AR 72205-7199.

centers of vascular surgery throughout Canada and the United States: Ottawa, Toronto, Detroit, Chicago, San Francisco, Los Angeles, Houston, Memphis, Baltimore, and New York. I was very interested to know what research in microvascular techniques was being performed. I described my own experiences in microvascular surgery of brain arteries in the animal laboratory in Burlington. I reported my results of the surgical removal of spinal cord arteriovenous malformations (AVMs) in 12 patients, on whom I operated from 1960 to 1965 at the neurosurgical department in Zurich, using conventional neurosurgical techniques which at that time did not include the use of the operating microscope or the bipolar coagulator. I emphasized that better surgical results could be achieved with microvascular techniques and bipolar coagulation. I also presented this lecture in the Neurosurgical Department of The Mount Sinai Hospital, New York. Sitting in the back of the room was a colleague, who kept smiling throughout my lecture. At the end, he stood up and said, "Gazi, I am Len Malis. I enjoyed listening to you, and I would like to tell you, first of all, that this type of spinal AVM surgery was performed in 1910 at The Mount Sinai Hospital by Dr. C. A. Elsberg. Second, I appreciated the fact that you are using my bipolar coagulator, which I constructed and manufactured years ago." Ever since then, in my publications and lectures, I have mentioned the importance of the bipolar coagulation technique and recommended that every neurosurgeon be familiar with the Malis coagulator.

I also visited Dr. J. H. Jacobson at The Mount Sinai Hospital and observed his vascular surgery performed in the hyperbaric chamber. He gave me three pieces of 9-0 suture, which I used during the following three months for reconstructive surgery in small brain arteries (1.0 mm diameter) of dogs.

On my return to Zurich in 1967, I began to apply microtechniques in the entire neurosurgical field, such as the reconstruction of occluded brain arteries, elimination of intracranial aneurysms, AVMs, cavernomas, extrinsic and intrinsic tumors of the central nervous system (CNS), and spinal surgery.

The microsurgical treatment of several thousand patients could only have been accomplished in combination with microvascular techniques, the bipolar coagulation technique, and the application of knowledge of microsurgical anatomy. Since 1964, in this latter respect, I have appreciated the work of Dr. Yun Peng Huang, who together with his teacher Dr. B. S. Wolf, initially, and then alone and with others, painstakingly described the course of arteries and veins along the fissures and sulci of the brain in many publications.

By the end of the 1960s, we had learned that it was not just the use of the operating microscope, but the combination of the above-mentioned three elements which was essential to improve conventional neurosurgical treatment of the various lesions of the CNS. Intracranial saccular aneurysms can be explored along the arachnoidal pathways. The course and anatomic variations of the parent arteries and perforators and their relation to the aneurysm wall can now be recognized in detail. Most aneurysms do not present with a real neck, but with a dysmorphic and bulging base arising from the ill arterial segments. This pathology must first be tamed and shaped using the bipolar coagulation technique. After creation of a proper neck, the final clip can be applied.

In AVMs, the parent arteries around the angioma can be dissected along the arachnoidal pathways, the feeding arteries identified, then coagulated with the use of the bipolar system and severed, and the AVM removed. Because the clipping technique for obliterating the feeding arteries can be avoided, the operating field remains clear and clean.

For the surgical treatment of extrinsic and intrinsic tumors of the CNS, the combination of microvascular techniques, bipolar coagulation, and the application of profound microanatomic knowledge enable the surgeon to perform exploration, debulking, shrinkage, and complete removal of the lesions.

I am very happy and proud to have had such a special relationship with my colleagues at The Mount Sinai Hospital, and as a neurosurgeon, I have always trusted the professional advice of Dr. Leonard Malis. I respect and admire his intelligence and integrity.

Reference

1. Jacobson JH, Wallman LJ, Schumaker GA, et al. Microsurgery as an aid to middle cerebral artery endarterectomy. J Neurosurg 1962; 19:108–114.

Leonard I. Malis:

An Appreciation

Lawrence Kruger, Ph.D., and Aaron J. Berman, M.D.

We first met Leonard Malis when he was a Dazian Research Fellow from Mount Sinai after his final year of residency training. One of us (LK) was a Ph.D. candidate and the other (AJB) was a research fellow in Professor John F. Fulton's laboratory at Yale University in 1949. At that time, Professor Fulton's laboratory was the mecca for neuroscience and attracted a variety of highly talented people. It was apparent to all of us, however, that Leonard was more than talented; he was truly gifted.

There were many wonderful attractions at Yale which were housed in Fulton's Physiology Department. There was the tumor registry and the marvelous neuropathology collection, a legacy of Harvey Cushing. After Dr. Cushing's demise, these were continued with loving care by the young assistant that Cushing had ushered into medical school, the devoted and ever gracious Louise Eisenhardt, who at that time also edited the Journal of Neurosurgery.

The "Fulton Lab," as the Physiology Department at Yale was known worldwide, possessed rare qualities, imbued as it was with the unique graciousness and style of John Fulton. Once each week there was a seminar, usually involving someone invited personally by Professor Fulton. The invited speakers during the Malis sojourn at Yale ranged from neurosurgeons, such as Sir Geoffrey Jefferson, to neurophysiologists, including Nobel laureate E. D. Adrian (later Lord Adrian and President of the Royal Society), George Bishop, and a long list of luminary physiological and neurological researchers. It was a time when it was still possible to follow all the major advances in work on the nervous system, unimaginable as that may seem today.

Although some of the clinician fellows were attracted to behavioral and neurological studies in primates after a variety of neurosurgical interventions, Leonard had a decided bent toward technological innovation and a passion for electronics. The challenges of electrophysiology were clearly his metier, and some of his attraction to the area was his recognition of the inferior design of the differential amplifiers and oscilloscopes then commercially available. The fact that he had access to an excellent machine shop and to electronic facilities where he was welcome and where he could work day and night must have clinched the commitment. Certainly, this experience was seminal in launching a life-long career in technological innovation, with particular emphasis on the needs of neurosurgeons.

Of course, Leonard had already revealed extraordinary precocity. He was born in 1919 in Philadelphia, but was raised and received his early education in Atlantic City. He was editor-in-chief of his high school newspaper, and he was regularly suspended from school for offending the principal. He compiled the highest absence record of any person in his graduating class, much to the surprise of his chemistry teacher, whose class he had never missed.

Before the age of 13 years, Leonard had designed and built a 500-watt radio transmitter and earned his "ham" license, built auto and boat engines (including work on Guy Lombardo's famous Tempo VI racer) before the age of 15 years, and built his first television set before there was any commercial television. Note that this is a partial

---

Address reprint requests to Lawrence Kruger, Department of Neurobiology, UCLA Medical Center, 10833 Leconte Ave., Los Angeles, CA 90095-1763.

list of the achievements of a nonconforming youth who spent much of his time and skills repairing pinball and other gambling machines in the Atlantic City area, thus providing the financial base for his college and medical school studies.

The Ventnor Boat Company, the leading producer of racing power boats at the time, was near Leonard's home. He spent many afternoons there, after or instead of school, helping to plank the hulls or assisting the race engine mechanics, in return for which he was occasionally allowed to drive. He was able to purchase and rebuild an older race boat with which he competed successfully for several years.

Leonard attended the University of Virginia, taking a specialized B.S. in chemistry, which did not include the biological courses required for premedical studies. Undaunted, he completed his college work in 3 years by virtue of the unlimited cuts permitted to holders of intermediate honors and to members of the Dean's List, while simultaneously taking the needed biology courses outside of the degree program and working in a laboratory provided by Dr. William A. Kepner, Professor of Biology. He continued to use this laboratory through medical school, at the University of Virginia, studying the basic cellular effects of short-wave radiation. Interestingly, the presentation of this study was announced on the Associated Press wire with the headline, "Virginia Scientist Invents Death Ray." In the course of this work, Leonard developed into a competent microscopist, photographer, and optics designer. He constructed all of his own equipment, including radio wave generators, thermocontrol systems, special illuminators, manipulators, and photographic units. He was elected to Alpha Omega Alpha in 1943 for his medical school academic standing.

In 1942, while he was still attending medical school, Leonard married. During the succeeding years, he and his wife, Ruth, had two children, Larry and Lynn. Today, they also have three grandchildren.

After receiving his M.D. degree in December 1943, Leonard interned at the Philadelphia General Hospital and then entered the army, becoming a captain in the Medical Corps. Presumably because of his interest in neurosurgery, certainly without formal training, he became the head of his hospital's neurological service by the war's end. He claims that the ignorance that he brought to this experience convinced him that a solid neurological background was essential for his future neurosurgical training. Upon discharge from the army, he was accepted into a residency in neurology with Dr. Israel Wechsler at the Mount Sinai Hospital. There was a delay of 10 months before the position would be open, however. These 10 months were spent as a general practitioner in Atlantic City. Leonard recalls this period as "an invaluable learning experience and the unhappiest time of my life."

After completing the residency in neurology, Leonard became Dr. Ira Cohen's resident in neurosurgery. The two services were essentially conjoined during that era and he virtually revered both Ira Cohen (who had been Elsberg's associate) and Israel Wechsler. On his retirement, Dr. Cohen presented his neurological and neurosurgical library, as well as his office desk and chairs, to Leonard, gifts that Leonard still treasures.

During his residency, Leonard participated in developing the new technique of myelography. Pantopaque had been introduced during the war years but was used in very small quantities. He developed a "full column" technique of myelography, published in 1953, by which he changed a most inaccurate method into a highly accurate means by which to visualize lumbar lesions. Cervical studies were rarely done at that time, except in the presence of a complete block. Leonard's work on myelography of the region of the foramen magnum, published in 1956, was one of the first demonstrations of safe and reliable evaluation of this area.

After finishing these residencies, Leonard started his fellowship year with Dr. Fulton, with support from the Dazian Foundation. During his first months at Yale, before suitable electronics could be designed, built, and tested for electrophysiological studies on the afferent projections to the precentral "motor" cortex, Leonard used the excellent Yale Medical Library to find the original papers of Arnold and Chiari for a paper he was writing on the Arnold-Chiari malformation (1). He also started the first design for a cassette changer, to supplant the single-cassette techniques then in use for carotid angiography and to bring neuroradiology into the era of high-resolution serial cerebral angiography. Unfortunately, this first design was unsuccessful; the clutch design for the huge wheel array proved incompatible with vibration-free frames at better than one frame per second. It was not until the following year, when he returned to Mount Sinai, that Leonard completed the design and constructed the first successful high-resolution automatic cassette changer for serial cerebral angiography. This single prototype machine was used at Mount Sinai for more than 250,000 films before it was finally retired.

During this same period at Yale, the unsatisfactory qualities of the currently used large Bovie electrocautery units and the improper use of "grounds" and "indifferent electrodes" in electrophysiology prompted Leonard to develop bipolar forceps with the appropriate electronics for their use, a device that is now an indispensable tool of modern neurosurgery throughout the world. This was the first of many innovations to bear the Malis eponym.

From conception to design, construction, testing, and ultimate application, the process of Leonard developing instrumentation was a joy and wonder to observe. His legendary ambidexterity in the surgical suite was no less impressive in the machine shop. Leonard was in constant demand for his multitudinous skills during this period, and with what he called the "easy" pace provided by his not doing surgery, he could be generous with his time and his help to others. He cared for Dr. Eisenhardt's fish across the hall when she was away, and mused over the tape loops with which Dr. Ernest Sachs, the aging pioneer neurosurgeon down the hall, was trying to teach mynah birds to talk before performing cerebral ablatons. Leonard offered advice and help, wanted or not, then as now, with a unique blend of intelligence, practicality and good humor.

By the spring of 1950, life was rich and full. Leonard presented his first research paper to the American Physiological Society in Cleveland, demonstrating a Rolandic cortex projection rostral to and independent of the postcentral tactile cortex (2)—everything being built was actually working. Forays into improving macrophotography and using a dissection microscope were to have substantial impact on his subsequent career development. He also began electrophysiological studies of the geniculostriate system in cats and brought one of us (LK), a young graduate student, back to Mount Sinai to jointly pursue the enigmatic problems of photic potentiation of the electrically evoked response and its implications for the theories of color vision extant at that time (3).

The period in New Haven opened new avenues for Len, but, most importantly, his world of personal contacts in both neurophysiology and in neurosurgery expanded significantly; lifelong friendships, as well as the bases for periodic collaborations, were established. We shared the pleasure and privilege of being a small part of that formative period in Leonard's career.

Returning to Mount Sinai to join the attending staff and to establish a laboratory was not easy task. His laboratory space consisted of a small room hidden away on the sixth floor. His previous mentors, Ira Cohen in neurosurgery and Israel Wechsler, were leaving. Cohen's illness and subsequent demise were especially painful. The new chief of Neurology, the indomitable Morris B. Bender, was a dominant force in the hospital, with a spirited and open antipathy to neurosurgery. The newly recruited chief of neurosurgery, Leo M. Davidoff, was not finding it easy either. But there were some important positive forces, especially the dynamic Bernie Wolf's radiology service, the brilliant physicist Sergei Feitelberg, and a talented young resident in neurosurgery, Peng Huang, later to be internationally acclaimed in neuroradiology, who became a lifelong colleague and friend.

The basic research laboratory was Leonard's principal focus at the time. His contributions to basic research in the next decade included two brief adventures of escape from the daily demands. Both of these involved one of us (LK) and are thus presented as a personal narrative. The first was something of a failure, but was a spectacular episode. Before going to Johns Hopkins as a postdoctoral fellow in 1955, I had obtained two dolphin brains for anatomical study at the new Marineland near St. Petersburg, Florida, the director of which, F. G. Wood, Jr., had been a fellow graduate student at Yale. This contact provided an opportunity to work with dolphins to enable mapping of the sensory areas of the extensive and elaborately convoluted cerebral cortex of these remarkable mammals. At a cocktail party for Clinton Woolsey at the home of Jerzy Rose, the idea for an "expedition" to Florida was conceived, and was ultimately planned in detail for the following year. The "team" from Baltimore consisted of Jerzy Rose, Vernon Mountcastle, and myself, and from Madison, Wisconsin, Clinton Woolsey and Joe Hind. Woolsey insisted we also bring someone experienced in respiratory physiology who would assume responsibility for building and operating a ventilator, and invited John Lilly from the National Institutes of Health. As instigator of the whole expedition, I insisted we bring experienced, competent neurosurgeons and invited Leonard Malis and Karl Pribram to join us. We assembled in Florida and it soon became obvious that, in building a functional laboratory, no one could surpass Leonard. The electronics for stimulation and recording, all designed by him, were brought from his laboratory at Mount Sinai, and Leonard rapidly assumed leadership. He became primary neurosurgeon, with Woolsey, Mountcastle, and Pribram serving as surgical assistants.

We did not achieve our ultimate experimental goal, principally because of problems with anesthesia, but some recordings of cortical activity were made from the dural surface of dolphins for the first time, and a path was paved for the future. The brains were taken to Johns Hopkins for morphological studies that were subsequently published and John Lilly air expressed in an Ampex tape deck, initiating his acclaimed studies of dolphin vocalization, drawing upon the several sounds that Wood and his co-workers had already related to specific behaviors. Another less imposing attempt was made several years later in San Diego with Ted Bullock from University of California, San Diego, but a proper sensory map of the dolphin still had not been achieved, although Leonard's reputation in this area was certainly established among the cognoscenti of sensory electrophysiology.

The other adventure was a rather extraordinary example of a scientific advance that could not have occurred without the special qualities of a Leonard Malis. In an attempt to destroy the layers of the cerebral cortex from the surface to different depths (for the purpose of anatomically determining the laminar termination of thalamic neurons), Jerzy Rose and I had explored several methods of laminar destruction, each was somewhat efficacious, but none were satisfactory because of a large gradient zone from the normal to the damaged sector. Confronted with successive failures, we posed the problem to Leonard on a visit to New York. His response seemed "off the wall" at first, but was logical. If you could get a monoenergetic beam of ionizing radiation, the particles should all stop at the same depth in a medium of homogenous atomic weight and, assuming that at first approximation brain could be calculated as water in terms of mass, it should be a simple matter to determine what energies and particles would be suitable. Ah, easy for Leonardo or the rarified world of polymaths, but surely not for ordinary mortals.

A few days later Leonard phoned to say that some rough estimates suggested that positively charged particles in the 20 to 30 million electron volt range should do the trick, but unfortunately that would require access to a fairly large linear accelerator or cyclotron, something that clearly did not exit in Baltimore or New York. But he said that, as a matter of curiosity, he had initiated inquiry into the availability of the 60-inch cyclotron at the Brookhaven National Laboratories. The details, although interesting and amusing, are beyond the scope of this narrative. However, it was an adventure into the lofty world of particle physics that would intimidate any biological scientist and even the most secure and self-confident of surgeons, except for Leonard Malis. Jerzy Rose and I both thought he was probably "nuts," but we could not resist admiring his imagination and logic; we agreed to process the brains if the appropriate radiation could be performed. Leonard quickly swung into gear, designed and built a gun-sight device for aligning a proton or deuteron beam and intuitively devised an ionization chamber for particle measurement, because beam current measurements were in a range for which the cyclotron laboratory was not equipped. The initial device turned out to be crude and alinear, resembling Pierre Curie's original ionization chamber. Len corrected its deficiencies, but not until after the first experiment on two cats, based on rough calculations that erred by a factor of about 18 (as we later learned). As luck would have it, the result was "on the money," and a spectacularly successful gamble paid off. Not only was the fuzzy line between intact and destroyed neurons about 10 μm, the size of one neuron, but it also proved possible to take out a layer in the middle (or several for that matter) without damaging overlying layers or the pial vasculature. When the first brain was cut at Johns Hopkins and I excitedly phoned Leonard in New York to tell him that a layer a few tenths of a milliliters thick was missing from the middle of the cortex, I received the classic Malis response: "Of course!" Perhaps extremes of self-confidence in the face of uncertainty is the *sine qua non* of a great surgeon, but in the world of real science this seemed a bit much. Of course, a short article was quickly submitted to *Science.* This 1957 paper (4) provided the first description of the use of the Bragg peak energy release in neural tissues. A massive project soon emerged and hundreds of lesions were made, providing the earliest accurate information on neuronal and glial radiosensitivity in precise physical units, supplanting previous biological units. The detailed report on the method and the quantitative radiobiology (5) was only the beginning of a series of papers revealing luxuriant regrowth of damaged cortical axons when the radiation dose rate was low enough to avoid the extensive gliosis accompanying all other kinds of experimental (or "natural") lesions (6). These were followed by anatomical studies of thalamic retrograde atrophy and intracortical degeneration which provided a new level of precision in determining functional laminar patterns in the cerebral cortex (7–9).

At that time, at Mount Sinai, no neurosurgical procedures were being performed under the microscope, although microsurgery of the middle ear was a regular procedure on the otologic service. However, in his college laboratory at the University of Virginia, Leonard had used the binocular dissecting microscope to manipulate the small organisms (microstoma) that had been the subject of his research. In the neurophysiology laboratory at Yale, it became apparent to him that vizualization with the naked eye did not permit adequate manipulation of cortex and microelectrodes. Leonard had purchased his first laboratory operating microscope in 1955 and, from then on, had used it for most of his laboratory dissection, developing instrumentation and modifying the microscope as its use increased.

In 1965, while operating on a youngster with a large solid craniopharyngioma, Leonard found a prefixed chiasm with only enough room between the optic nerve and the carotid for a minimal biopsy. He had the microscope brought into the operating room and, using a series of otologic instruments together with his own animal laboratory instruments, was able to achieve an apparently complete removal.

This event totally changed his direction. He realized that a technical revolution in neurosurgery had to occur. During the next 2 years, he closed down the electrophysiological research program and put his efforts into designing and constructing prototype instruments in his basement shop and modifying the microscope through adaptation of early television systems. By 1968, Leonard was able to give the first of a series of courses in microneurosurgery at the hospital. There were 40 operating microscopes in the demonstration laboratory, with rabbits under anesthesia at each scope and a team of four surgeons rotating at each station. The units were linked by closed-circuit television to the instructor's scope. In this program, he had the teaching collaboration of the pioneering microneurosurgeons, Drs. Donaghy and Yasargil. These highly successful programs continued until 1975, when Leonard felt that the microtechnique had become such a part of every training program that they were no longer needed.

The advent of microprocessors permitted Leonard to design a bipolar coagulator which could produce exactly the wave-form variation desired, but which had been unobtainable with either spark or previous solid-state equipment. This unit was a major improvement over previous instruments because of reduced sticking and charring, much smoother coagulation and virtual absence of sparking at the forceps tips. Leonard's brother, Jerry, formerly a research pharmacologist, set up a manufacturing company to produce these units.

At Mount Sinai, Leonard developed a unique operating room television network, linking the neurosurgical operating rooms, neurosurgical offices, laboratories, and the neuroradiology section. Much of this network, first installed in 1967, was of his own design and construction.

In the years that followed Leonard's appointment as Chairman, the Neurosurgical Department at Mount Sinai doubled in size, going from one available operating room with one operating room nurse to two totally dedicated operating rooms with a full support suite and eight neurosurgical specialist nurses. Research and teaching space was increased from a single laboratory to eight laboratories, in addition to shop, photographic, and conference rooms.

As the strength of the other attending neurosurgeons grew, Leonard was able to limit the operative cases he accepted to angle tumors, clivotentorial and parasellar tumors, intramedullary tumors of the spinal cord, and arteriovenous malformations of the brain and cord. All of these procedures were entirely microsurgical, of course, and all were planned for total removal. His extensive experience with total removal of meningiomas and his close to zero recurrence rate are testimony to his innovative approach and legendary operative skills. He achieved total resection in more than 600 consecutive acoustic neuromas, and he was able to preserve useful hearing in 50% of the patients with preoperative useful hearing.

Leonard's department was always one where the lights burned at all hours. His staff was devoted to him and to his programs, so that attending physicians, nurses, psychologists, and residents would still be at work on the basic and clinical research problems long into the night. He was, and still remains, a stimulating, iconoclastic, and original teacher.

Even in a climate pervaded by the threat of litigation, he was always totally honest in seeking the causes of any failure and stressing possible future preventative measures. He has always been a kind and gentle mentor, rarely raising his voice or becoming obviously angry. Speaking quietly, he could be devastatingly critical of a particular course of action, but then might add that he was sure that the person he was criticizing would have made the correct decision had the x-ray film been of better quality, or offering some other exculpatory explanation.

While still in practice, Leonard found time to make eight to ten trips a year as an invited guest speaker. His lectures were illustrated by his own photography and were considered an outstanding feature of any meeting, always drawing large audiences. He was honored as the Olivecrona Lecturer in Stockholm and the Krayenbuhl Lecturer in Zurich, and he received the Jacobi Medallion from the Mount Sinai Alumni in 1983. He was the honored guest of, among others, the Japan Neurosurgical Society, the Swiss Neurosurgical Society, and the Mexican Neurosurgical Society, and he was also visiting professor at several universities. He is a member of numerous prestigious professional associations, including the Academy of Neurosurgery, the Society of Neurosurgery, and the Society of Neurological Surgeons. He is an Honorary Member of the Canadian Neurosurgical Society and of the Japan Neurosurgical Society.

Leonard's career has been imbued with a spirit of discovery and innovation that derived from his background in science. He was fully prepared to participate in what proved to be an extraordinary era in neurosurgery, and he brought to this field extraordinary gifts and scientific insights, together with a passion for devising new techniques and new tools. He led, and continues to lead, a full, productive, and energetic life. He combines compassion and tenderness with dedication and a rigor of intellect to which most of us aspire but few can attain. The field of neurosurgery has been enriched by his many contributions; his colleagues and friends are enriched by his companionship.

References

1. Malis LI, Cohen I, Gross SW. Arnold-Chiari malformation. Arch Surg 1951; 63:783–798.
2. Malis LI, Pribram KH, Kruger L. Action potentials in "motor" cortex evoked by peripheral nerve stimulation. J Neurophysiol 1953; 16:161–167.
3. Malis LI, Kruger L. Multiple response and excitability of cat's visual cortex. J Neurophysiol 1956; 19:172–186.
4. Malis LI, Loevinger R, Kruger L, Rose JE. Production of laminar lesions in the cerebral cortex by heavy ionizing particles. Science 1957; 126:302–303.
5. Malis LI, Baker CP, Kruger L, Rose JE. Effects of heavy ionizing monoenergetic particles on the cerebral cortex. I. Production of laminar lesions and dosimetric considerations. J Comp Neurol 1960; 115:219–242.
6. Rose JE, Malis L, Kruger L, Baker CP. Effects to heavy ionizing mono-energetic particles on the cerebral cortex. II. Histological appearance of laminar lesions and growth of nerve fibers after laminar destruction. J Comp Neurol 1960; 115:243–296.
7. Rose JE, Malis LI. Geniculo-striate connections in the rabbit. I. Retrograde changes in the dorsal lateral geniculate body after destruction of cells in various layers of the striate region. J Comp Neuro 1965; 125:95–120.
8. Rose JF, Malis LI. Geniculo-striate connections in the rabbit. II. Cytoarchitectonic structure of the striate region and of the dorsal lateral geniculate body; organization of the geniculo-striate projections. J Comp Neurol 1965; 125:121–140.
9. Kruger L, Malis LI. Distribution of afferent and efferent fibers in the cerebral cortex of the rabbit revealed by laminar lesions produced by heavy ionizing particles. Exp Neurol 1964; 10:509–524.

Technical Contributions of Leonard I. Malis

Jerry L. Malis, Ph.D.

Editor's note: Jerry is Leonard Malis's younger brother. He was trained in pharmacology and physiology. At Wyeth Laboratories, he was responsible for research in neurophysiology and neuropharmacology. His main areas of interest were the central pathways of pain and the pharmacology of narcotic and nonnarcotic analgesics, and he has many publications in these areas. Jerry Malis left as senior research scientist in 1978 to form the Valley Forge Scientific Corporation and to manufacture the bipolar coagulation systems designed by Leonard Malis. He is now the president and chairman of the corporation which develops medical devices for health care markets and is the leading supplier of electrosurgical equipment to hospitals all over the world.

I AM IN A RATHER UNIQUE POSITION. During the past 60 years I have been a student, recipient, beneficiary, collaborator, test subject, and, in some cases, a victim of Leonard Malis' technological creations and soaring intellect. Of course, being his little brother, as he referred to me until well after my 50th birthday, has given me an ideal seat from which to observe the broad spectrum of his intellectual gifts.

Leonard's technological bent was evident at a very early age. At 12 years of age, he was one of the youngest ham radio operators in the United States. At 15, he had designed and built a 1000-watt transmitter, the most powerful an amateur operator could own, and installed it in his bedroom with little space for anyone to enter, because the open racks went from floor to ceiling. He was able to talk with radio operators around the world and, because communication was better at night, got very little sleep. Unfortunately, Leonard soon learned one of the disadvantages of not being an only child. Because we lived in a two-bedroom apartment, I had to share a bedroom with him. I was then 3 years old. When our mother realized the very high voltages used in his open frame transmitter, the transmitter or I had to go. Although Leonard put up really great arguments, Mom finally won out and I stayed. Not totally thwarted by this event, he scavenged parts from his transmitter and designed and built one of the earliest high-powered, high-quality sound systems, which he rented out for various private functions and to some of the night clubs in Atlantic City.

Throughout his high school years, Leonard had the distinction of being absent 89 times each year. Because state law mandated that 90 days of absence per year would require him to repeat the year, he skirted the edge. Nevertheless, he was the editor of the school paper and the commencement speaker for his class. Also at about this time, his knowledge of electronics and mechanics led to another commercial foray. He sold his services as a master repairman to the operators of the boardwalk amusement arcades, repairing various pinball machines, and even take-your-own-photo machines. He was then about 16 years old, and Atlantic City was still in its heyday. Illegal, but protected gambling establishments were everywhere. Leonard was approached and asked if he could repair slot machines or one-arm bandits. Being Leonard, and never having seen the inside of a slot machine, he of course said yes. Soon afterward, at about 9:00 one night, two large men in black suits appeared at our door. They took Leonard to a large warehouse room filled

---

Address reprint requests to Jerry Malis, Valley Forge Scientific Corp., 136 Greentree Road, Oaks, PA 19456.

with slot machines. He worked on them through the night, learning as he went, and had them all working by morning and was paid $200, a huge sum in the middle of the depression. He continued this arrangement weekly, until he went off to college carrying his tool kit and tube tester. Each summer, however, he returned to his service business.

At the University of Virginia, first as an undergraduate and then as a medical student, he made a research proposal and was given a laboratory in the Department of Biology. He studied the effects of high-frequency radiation on basic cell mechanisms. He designed and built the radio wave generators, all the special optical, photographic, and light systems necessary for these experiments (Fig. 1). His early use of binocular stereoscopic dissecting microscopes paved the way for his future developments in adapting the microscope for surgical procedures. Parts of his research were picked up by the popular press and headlined: "Virginia Scientist Invents Death Ray." In the honors program he was allowed to take several courses simultaneously. Because the examinations were given on the same day, Leonard became very quick at taking tests. He completed his undergraduate work in 3 years, and was then admitted to medical school. I should note here that, with his supreme confidence, Leonard had applied to only one college and to one medical school. In fact, later on, he only applied to one internship, one residency, and one fellowship.

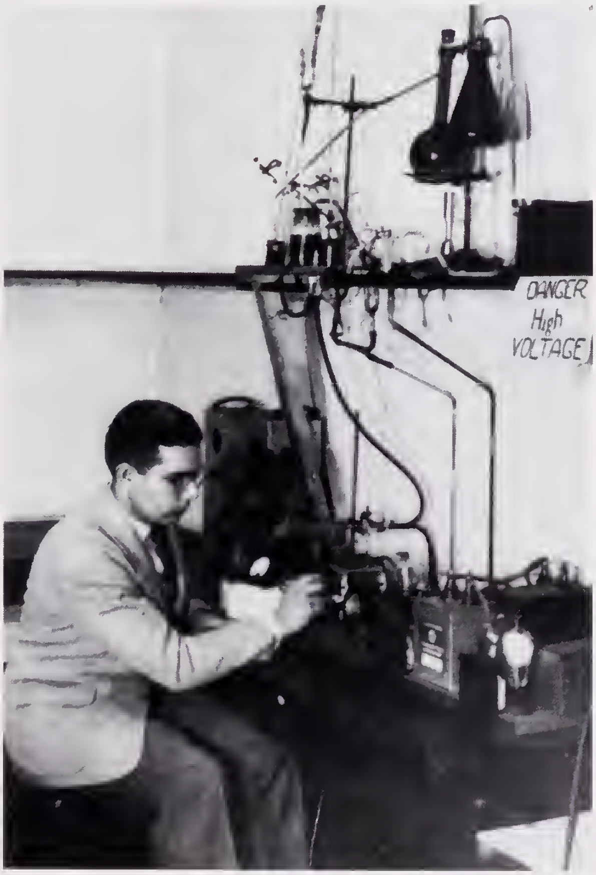


Fig. 1 Leonard in his laboratory at the University of Virginia, *circa* 1938.

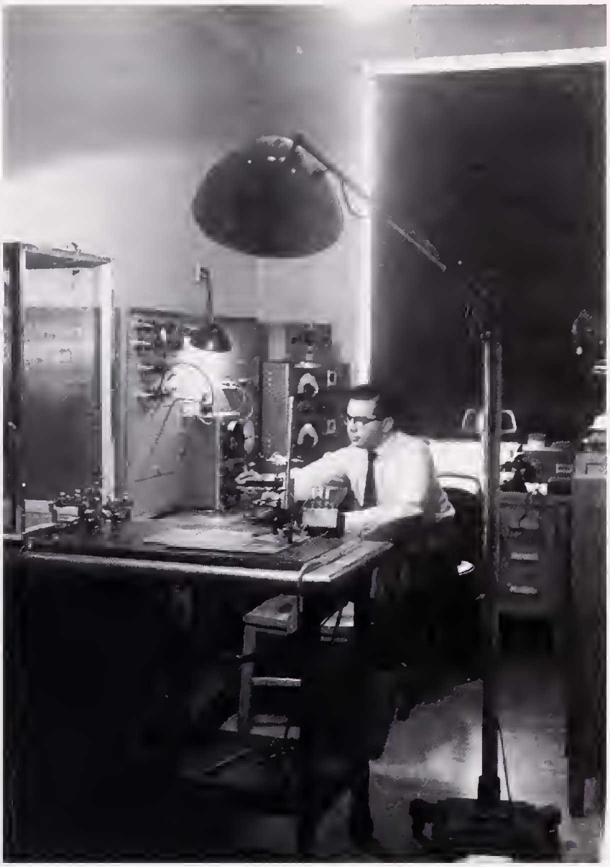


Fig. 2 Leonard in his first Mount Sinai laboratory in the old surgical pavilion, *circa* 1951.

After receiving his M.D. and serving as a captain in the medical corp, Leonard came to Mount Sinai as a resident, first in neurology and then in neurosurgery. On completion of his residency training, he had a 1-year fellowship at Yale in John Fulton's department, which at that time was the premier site for neurophysiological research. Leonard's major interest was thalamocortical projections and geniculate pathways. His early work in evoked potentials is frequently cited even today in neurophysiological literature (1, 2).

At the start of his Yale fellowship, he saw that the electronic equipment being used in the laboratory left much to be desired. In a matter of a few months, he designed and built a new set of physiological amplifiers which had extremely low noise levels and very high resistance to outside interference. He was unhappy with the current status of the art in ocilloscopes, so he designed circuitry that enabled him to do true dual beam recording with dual time bases. He also designed and constructed unique electronic stimulators which set a new standard. Some are still in use today, 45 years later.

When Leonard returned to Mount Sinai as assistant attending neurosurgeon, he was given a small space in the old surgical pavillion (Fig. 2) and built new, improved equipment. He later moved to a more spacious area in the department of physics. From these laboratories came a veritable flood of new instruments, devices, techniques, and, of course, publications. His total laboratory system was considered to be so superior that it was selected to be transported to Marineland in Florida to do electrophyisiologic studies of porpoise brain activity (Fig. 3). From his early work with stimulators and the isolation of their pulses, combined with his surgery in the animal laboratory, he saw the need to replace the standard monopolar coagulator. The Bovie had major disadvantages for use in the neurosurgical operating room. It had tremendous current spread because of its need for a dispersive electrode and a high impedance which made it useless

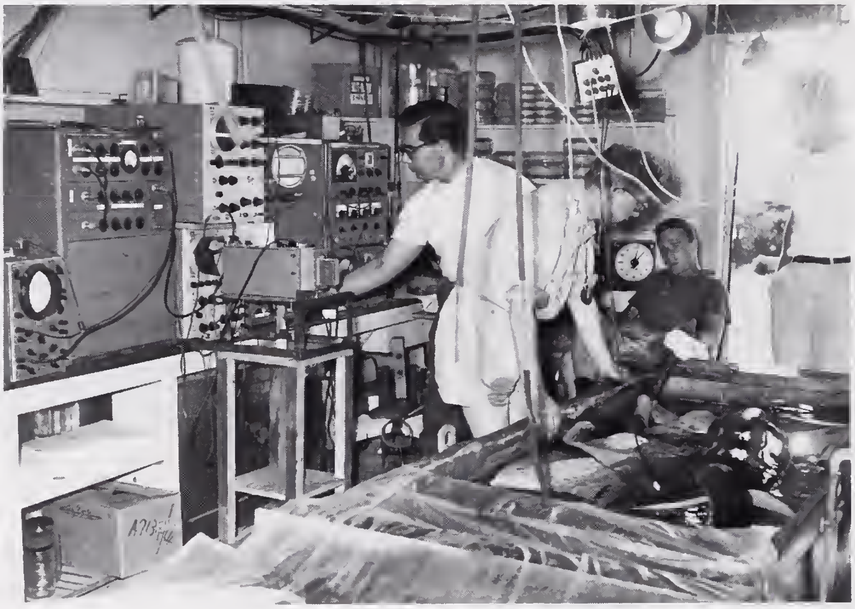


Fig. 3 Leonard's electronic laboratory equipment moved to Marineland in Florida to study the porpoise brain. From left to right, Leonard, Jerzy Rose, Larry Kruger, and John Lilly.

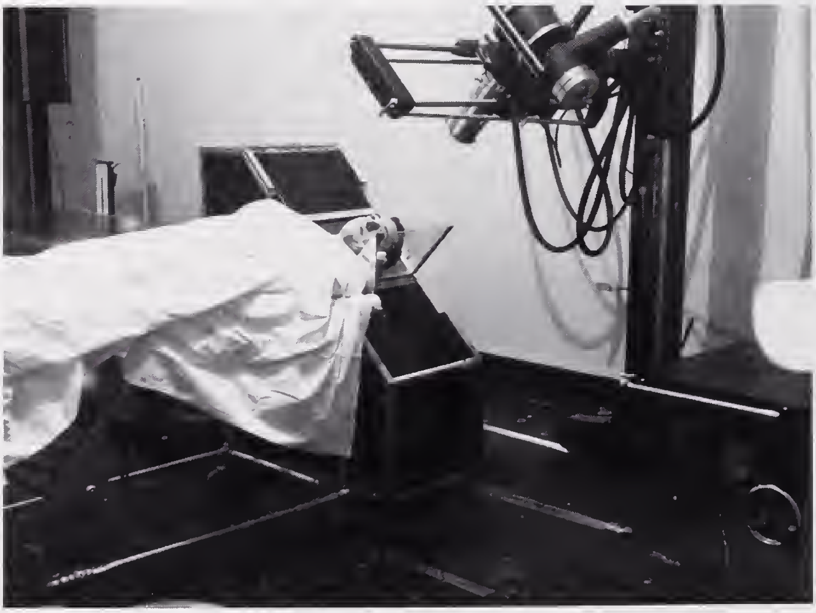


Fig. 4 Malis cassette changer positioned for AP cerebral angiogram.

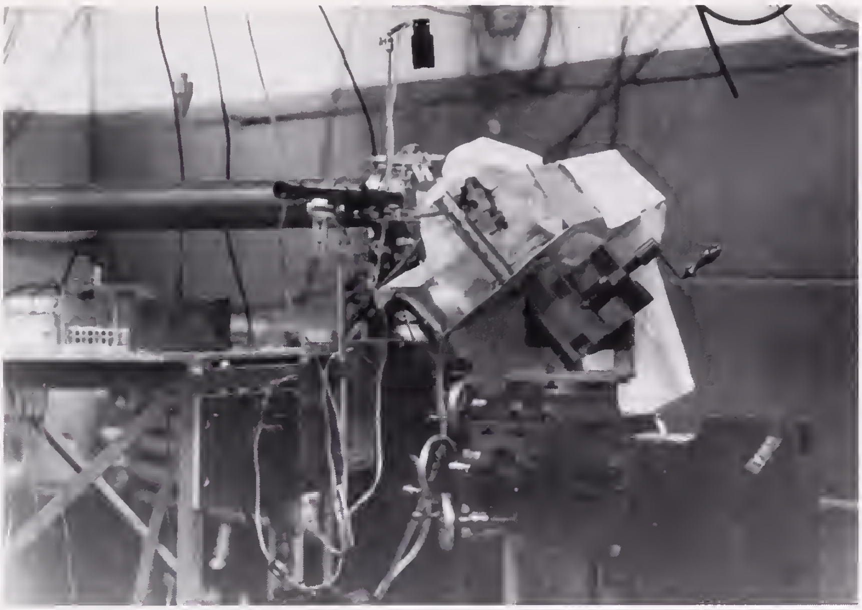


Fig. 5 Leonard's milling machine and rifle sight positioning the animal with cortex exposed at the end of the cyclotron beam pipe at Brookhaven National Laboratories.

in a wet field. Leonard wanted a true bipolar instrument with low-output impedance and precise coagulation. Working in his high-tech environment, mainly his basement workshop, he built the first of his spark gap machines and then the bipolar forceps. By using a spark gap to generate the power, he was able to obtain a better waveform for coagulation. With this forceps and the new generator all of the current passed between the forceps tips with no spread to adjacent tissue. Many of his original devices are still in use (3, 4).

It was about this time that Leonard began his association with the Codman and Shurtleff division of Johnson & Johnson. Codman took over the distribution of the coagulator and produced, on his design, a line of bipolar forceps. The original series was made of stainless steel. Later Leonard redesigned the forceps as well as many other instruments using titanium, another innovation (5, 6). His work with titanium and titanium alloys led to his development of the titanium mesh and acrylic cranioplasty, now widely used to replace skull defects (7). His continuing association with Codman represents more than 30 years of mutual respect.

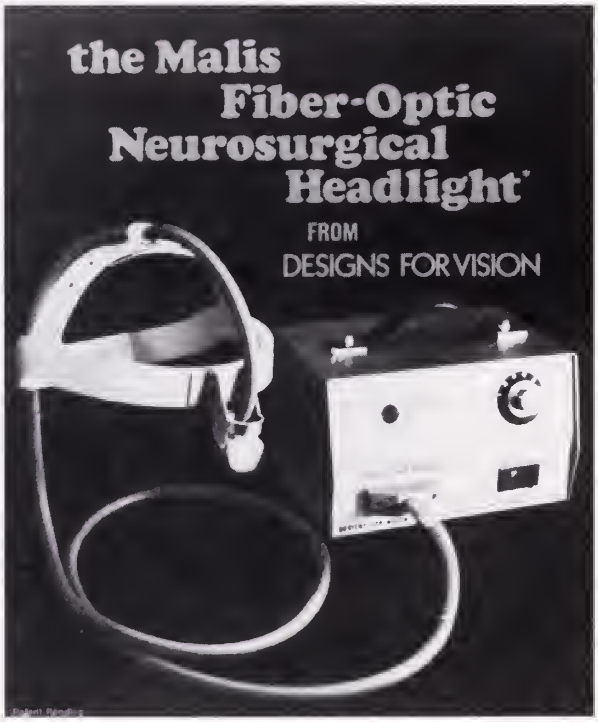


Fig. 6 Malis designed a fiber-optic surgical headlamp.

In 1950 the need for a practical method for serial angiography was evident because the single film per injection was completely unsatisfactory, as was the use of a cassette holder for several cassettes, pulled by hand with highly variable timing. Leonard decided to solve the problem. His first machine was designed using a wheel 4 feet in diameter with the cassettes inserted into its rim. It was power driven to go from cassette to cassette once per second. It was a self-destroying failure, because the momentum was too great to stop the heavy wheel in time, and it literally tore itself apart. He then built a unit which stacked seven lead backed standard x-ray cassettes, one of which was automatically pushed into a receiving bin each second, with automatic x-ray firing (8). This unit, installed in 1951, did all of the cerebral angiography in Mount Sinai and ran for more

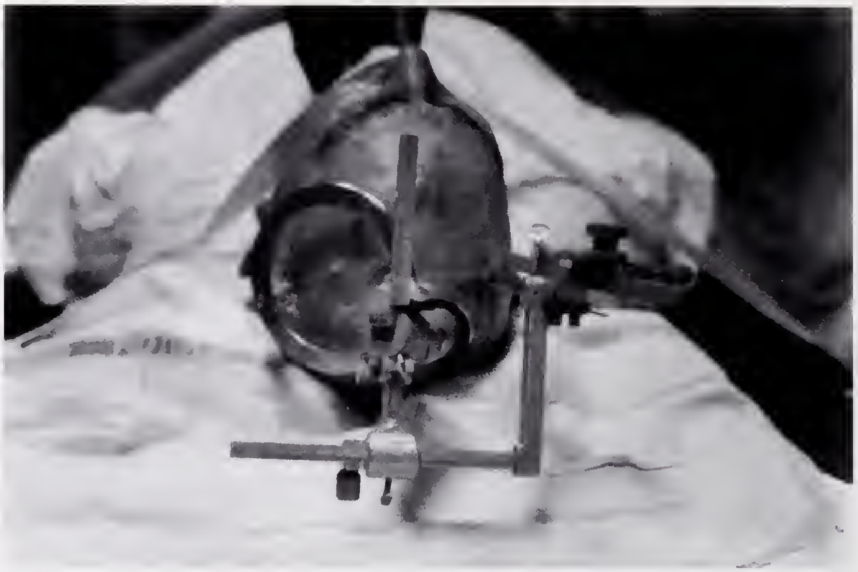


Fig. 7 Thalamotomy with Malis stereotaxic unit, *circa* 1954.

than 250,000 films during its lifetime, before it wore out to the point where maintenance was no longer feasible. Both anteroposterior and lateral projections were taken simultaneously without moving the patient. This was especially important in an era when angiography was done by direct carotid puncture (Fig. 4). The film quality was as good as any skull films done on the regular x-ray tables. Its only disadvantage was the very loud banging noise of the shifting cassettes, then most startling in the quiet of the radiology department, about as noisy as present day magnetic resonance imaging machines.

As an outgrowth of his early work in neurophysiology, Leonard's interest in functional differentiation of cortical layers led to a brilliant insight into the realm of radiation physics. He had been fascinated by some of the early work with beta particles and their very limited penetration in tissue. Investigating further, he found that the Brookhaven Laboratory 50-inch cyclotron produced particle beams of protons or deuterons. Leonard knew the physics related to the Bragg curve and postulated that using its peak energy release at the end of range might be the method to selectively destroy discrete cortical layers. This led him to precise energy measurements and calibration and was the first use of cyclotron radiation on neural tissue (9). His animal experiments during the next few years proved his theory and produced basic papers on cortical function (10, 11).

Leonard has always worked under the "kiss principle" (keep it simple, stupid). At Brookhaven, he required a method to properly align the beam and position the animal with extreme accuracy, and he came up with a system of elegant simplicity. He mounted the animal holder onto a used milling machine base which could be moved in any of three axes with total reproducibility. To spot the beam at the exact cortical area he built a prism system coupled to a rifle telescopic sight,

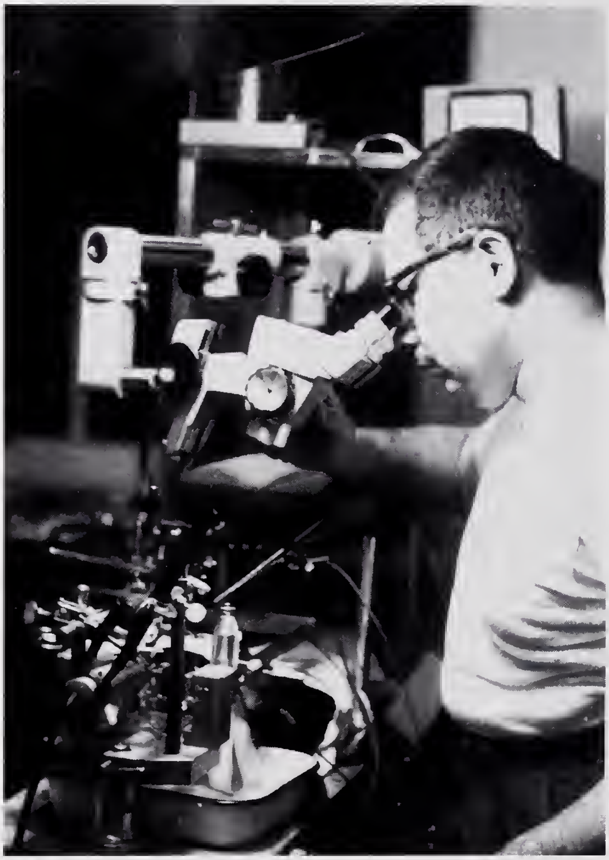


Fig. 8 Leonard using a binocular microscope to operate on an animal brain, *circa* 1955.

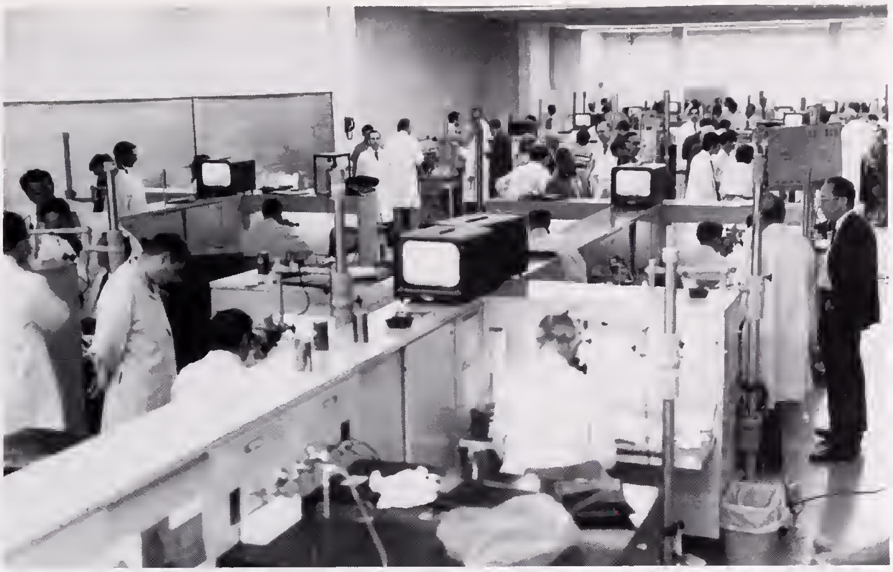


Fig. 9 The first U.S. microneurosurgical course, held in the basic science building at Mount Sinai, 1968.

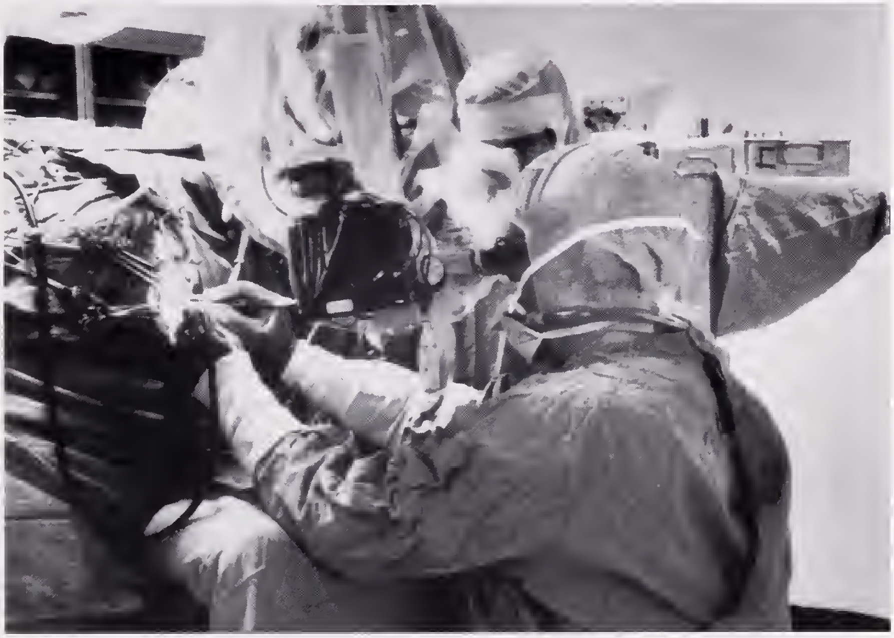


Fig. 10 Leonard carrying out microsurgical removal of an acoustic neuroma. He is using his bipolar coagulator and his 80-mm regulated soft suction. His elbows are supported by his own arm rest unit. A vacuum aspirator can be seen coming from his mask, preventing exhalation reaching the field.

which in turn was coupled to the milling machine base. The controls of the milling machine were used to move the animal to align the cross-hairs of the sight to the area desired (Fig. 5).

In the premicroscopic era as a teaching aid, Leonard designed and built a self-contained automatic camera system which could be safely used in the sterile field. A modified Robot camera, self-winding and with a ring flash and power supply he had designed comprised a unit which was then placed in a sterilized, four-legged case. After closing the case, the camera was triggered through membrane buttons. He had modified the optics so that perfectly focused pictures were taken by holding the case with the legs outlining the area to be photographed. Photographs from this camera were reproduced in many publications and formed the basis for many of his lectures. Unfortunately, the camera came to a bad end. Someone neglected to remove the camera from the case before putting it into the autoclave.

In that same period operating headlamps

used forehead-mounted bulbs, of high heat and low brightness. Leonard designed the fiberoptic head lamp which quickly became the virtual standard and is used in most operating rooms worldwide (Fig. 6).

When stereotaxic surgery was in its infancy, used only for treating Parkinsonism, the instruments were heavy and cumbersome, and took hours to set up. Going back to his years of experience in the animal laboratory where stereotaxic procedures were routine, Leonard designed a head-mounted stereotaxic system which could be properly positioned in minutes and weighed next to nothing. With his device, electrode placements were accomplished in brief, single-stage procedures (Fig. 7).

In his laboratory at Mount Sinai, Leonard had drawn on his earlier experience with binocular dissecting microscopes and had been doing most of the animal surgery and microelectrode placement under magnification (Fig. 8). In the mid 1960s he began to use the microscope in the human operating room. He developed instrumentation specifically designed for use with the microscope. He also began to modify the microscope for photography and for television. By 1968 he was able to direct the first microneurosurgical course in the United States, convincing the Zeiss Corporation to hold all microscope deliveries throughout the country for 3 months so that 40 operating microscopes were available for the program. From the central teaching microscope, television demonstrations were distributed to monitors at each of the consoles (Fig. 9). This program was repeated in 1971 and 1973 with more than 500 neurosurgical participants.

Leonard designed an optics system (Fig. 10) which allowed the television camera to see exactly the same field as the surgeon and a camera mount which allowed him to take color photographs of the surgical field (12). Because of his interest in teaching microsurgery he was not content with a television monitor only in the operating room. Leonard built a complete television and sound distribution system which connected the operating rooms to neuroradiology, the neurosurgical offices, the conference room, and the various neurosurgical laboratories. Even in his office, while deep in discussion, he kept an eye on what was going on in surgery. In the middle of a sentence, Leonard would sometimes pick up the microphone and, in his soft voice, say, “I wouldn't do that.” In the operating room, it sounded like the voice of God.

Because there were so many changes in position when using the microscope, Leonard became impatient with having to rely on someone to constantly raise and lower the stool. He finally took a used window motor from an old automobile and modified a stool which he could raise and lower in smooth motion with the touch of a foot switch, while seated. Again, as new and better drive systems became available, Leonard continued to modify his design, resulting in the totally self-contained, rechargeable battery-operated stool system in use today (Fig. 11).

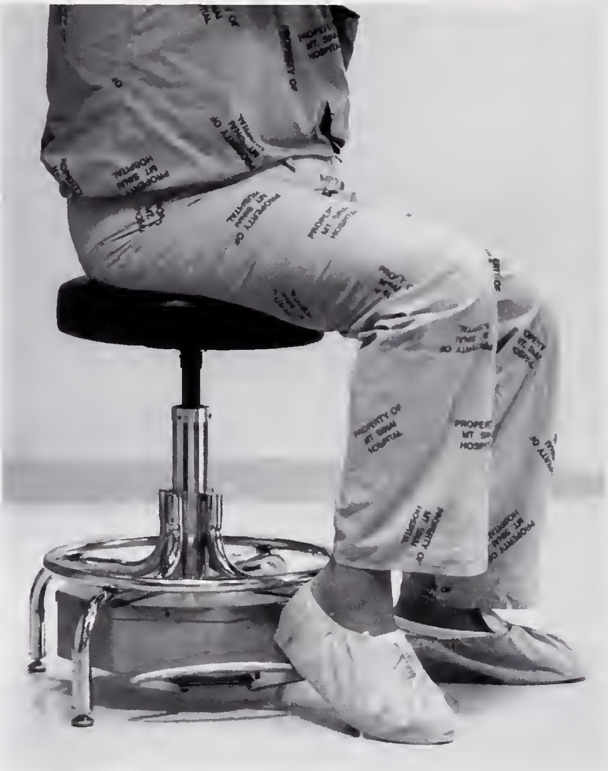


Fig. 11 Malis rechargeable battery-powered surgical stool.

In designing the new operating rooms in the Annenberg pavilion Leonard did not want the vertical ceiling columns proposed for anesthesia and power sources because they could interfere with future microscope placements and imaging equipment. He designed and built an umbilical system, which provided all anesthetic gases, suction connections, manifolds for mask aspirators, temperature-controlled water flows for warming and cooling blankets, air flow for pressure suits, high-pressure nitrogen for power tools, isolated and regulated electrical supplies, as well as television and monitoring cables. These units are still in use today (Fig. 12).

Leonard also designed and built one of the earliest evoked potential systems for use in the operating room (Fig. 13). The designs for the ultra-low level amplifiers were an extension of those he built for his laboratory studies, further developed to function even in the electrically noisy operating rooms.

With the advances in the manufacture of optics, he designed an entirely new set of magnifying loupes. His new design permitted edge to edge sharpness as well as extreme depth of field and highest light transmission, using triplet lenses instead of the usual Galilean system. He also designed a mount which did not require the loupes to be mounted through the lenses.

As the number of microsurgical procedures increased, Leonard became more and more aware of the need to improve on his original spark gap coagulator. Although years of experience had shown this unit to be the best available, the variations he wanted had not been technically feasible. With the advent of microprocessors and high-

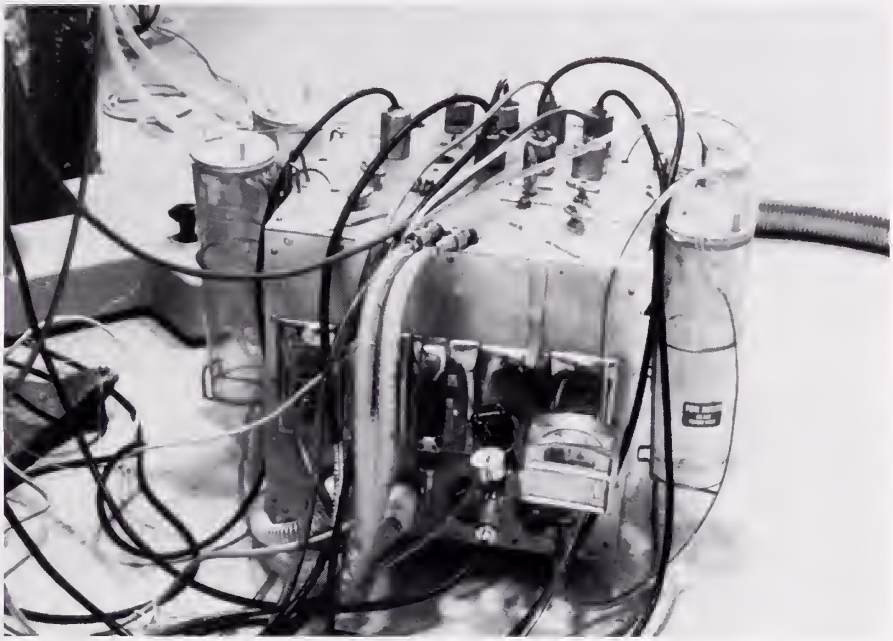


Fig. 12 Umbilical system which supplied all utilities and gases, as well as television and monitoring access to the operating fields. Leonard designed, built, and installed these when the Annenberg building was constructed. These units are still in use.

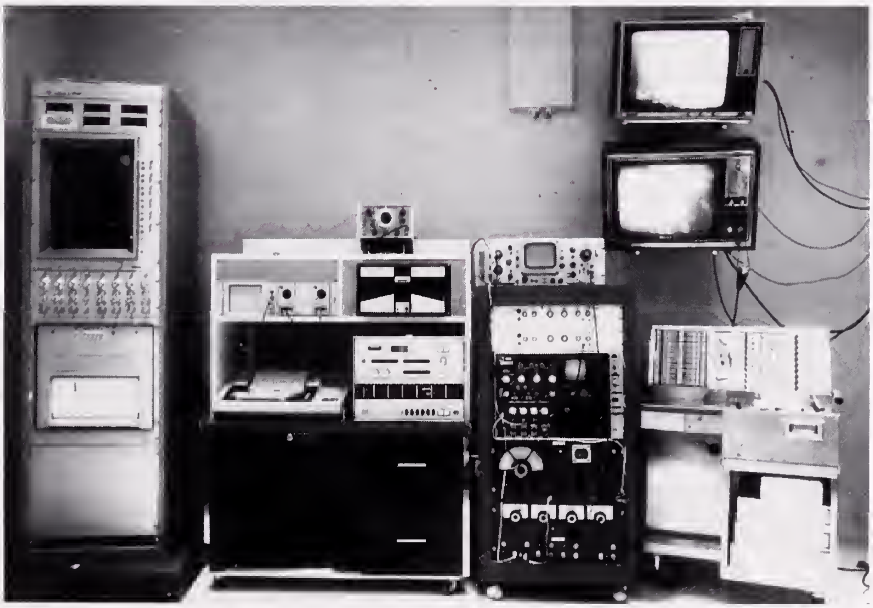


Fig. 13 Monitoring system in neurosurgical operating rooms, Annenberg building, *circa* 1977.

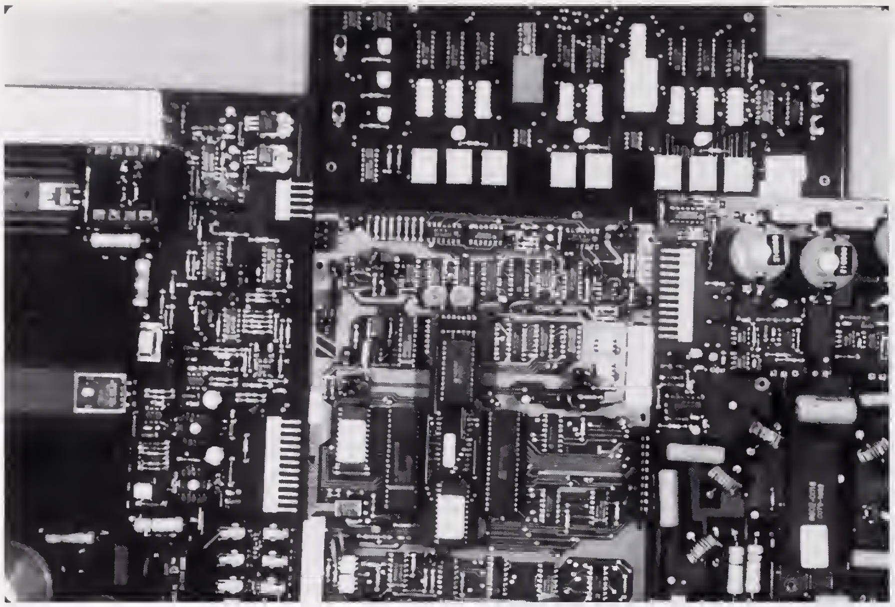


Fig. 14 Circuit boards of the CMC III, an indication of the complexity and sophistication of the modern generator.

voltage field effect transistors in the early 1980s, the time had come to design a coagulator with the exact features he wanted. The result was the Malis CMC II, with more than 4000 machines in use worldwide. With this unit, he had simulated the aperiodic waveform of the spark gap system and eliminated the high-voltage leading spike which had caused undesirable sparking and pitting of the forcep tips as well as forceps sticking and television and monitoring equipment interference. The computer control of the new waveform produced a damped asynchronous train. The microprocessor control provided not only aperiodic trains of pulses, but also varied the pulse width and frequency within the damped train. This synthesized waveform eliminated molecular resonance which, in periodic waveforms, produced unwanted cutting and perforation of vessels being coagulated. In addition, in the new design, Leonard was able to achieve a generator with the lowest possible output impedance. This feature allowed coagulation even when the forceps tips were submerged in saline or blood.

Leonard designed a self-contained irrigation system which could be used in conjunction with the coagulator. To deliver the irrigation at the forceps tips, he designed for Codman an entire line of bipolar irrigating forceps. As is the case with most of the Malis instruments, these are used worldwide.

With the advent of new and increasingly powerful integrated chips he was able to redesign the circuits to incorporate an entirely new modality to bipolar usage, the ability to do bipolar cutting. With this feature he could rapidly and bloodlessly cut and core tumors under saline irrigation, with no current spread or damage to adjacent areas. This advance in design led to another generation of Malis bipolar machines, the Malis CMC III. These units are rapidly becoming the state of the art in neurosurgery as well as other surgical disciplines, with 1500 already in use (Fig. 14). To fully utilize the cutting feature, he added additional forceps patterns specifically designed for bipolar cutting.

Leonard continues to be totally involved with new concepts in equipment and instrumentation. His renown as a surgeon, innovator, and teacher is truly international.

References

1. Malis LI, Pribram KH, Kruger L. Action potentials of motor cortex evoked by peripheral nerve stimulation. J Neurophysiol 1953; 16:161–167.
2. Malis LI, Kruger L. Multiple response and excitability of cat's visual cortex. J Neurophysiol 1956; 19:172–186.
3. Malis LI. Bipolar coagulation in microsurgery. In: Donaghy RM, Yasargil MG, eds. Microvascular surgery. Stuttgart, Germany: Georg Thieme Verlag; 1967:126–130.
4. Malis LI. Hemostasis in microsurgery. In: Yasargil, MG, ed. Microsurgery applied to neurosurgery. Stuttgart, Germany: Georg Thieme Verlag; New York: Academic Press; 1969:41–47.
5. Malis LI. Instrumentation and techniques in microsurgery. Clin Neurosurg 1979; 26:626–636.

6. Malis LI. Instrumentation for microvascular neurosurgery. In: Fein and Flamm, eds. Cerebrovascular surgery. New York, Berlin, Heidelberg, Tokyo: Springer-Verlag; 1985:245–260.
7. Malis LI. Titanium mesh and acrylic cranioplasty. Neurosurgery 1989; 25(3):351–355.
8. Malis LI. An automatic cassette changer for cerebral angiography. J Mt Sinai Hosp 1957; 24:54–61.
9. Malis LI, Loevinger R, Kruger L, Rose JE. Production of laminar lesions in the cerebral cortex by heavy ionizing particles. Science 1957; 1266:302–303.
10. Malis LI, Baker CP, Kruger L. Effects of heavy, ionizing monoenergetic particles on the cerebral cortex. Production of laminar lesions and dosimetric consideration. J Comp Neurol 1960; 115:219–242.
11. Malis LI. Effects of laminar lesions on evoked activity in the visual cortex. In: Haley and Snyder, eds. Response of the nervous system to ionizing radiation. Second International Symposium. Boston, MA: Little, Brown & Co.; 1964:522–540.
12. Malis LI. Neurosurgical photography through the microscope. J Microsurg 1982; 3:168–175.
13. Malis LI. Electrosurgery. J Neurosurg 1996; 85:970–975.

Basic Science Contributions of Leonard I. Malis

PETER W. CARMEL, M.D., D.MED.SC.

Editor's note: Dr. Carmel completed his M.D. degree at New York University and took postgraduate training in general surgery at Bellevue Hospital. After his neurosurgical residency at The Neurological Institute, he earned a D.Med. Sc. degree at Columbia University. From 1970 through 1994, he held academic and professorial appointments in the Department of Neurosurgery at the College of Physicians and Surgeons. Presently, Dr. Carmel is Professor and Chief of the Section of Neurological Surgery at the University of Medicine and Dentistry of New Jersey. His bibliography includes more than 90 publications, and his curriculum vitae records major committee assignments in the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, the New York Society for Neurosurgery, and the American Medical Association.

A PIVOTAL YEAR IN Dr. Leonard Malis' training was the academic year 1950–1951. During this period he was a Research Fellow in Neurophysiology at the laboratory of Dr. John Fulton at Yale. Fulton was the preeminent neuroscientist of his day, and his laboratory was a very heady place, truly the neurophysiological "Mecca." The laboratory was filled with bright young researchers most of whom have become leaders in the field during their careers. The group included Don Baron, John Broback, Karl Pribram, Larry Kruger, and Bob Livingston. Malis prospered with this intellectual elite, using both physiological and anatomic methods in an attempt to dissect complex functional systems. This effort would engage him for more than the next 15 years.

The first problem to which he devoted his attention was investigation of sensory evoked potentials in the primary motor cortex. The report of this work was the first article of the neurophysiological publications with Malis as the first author (1). He stimulated the cut sciatic nerve in

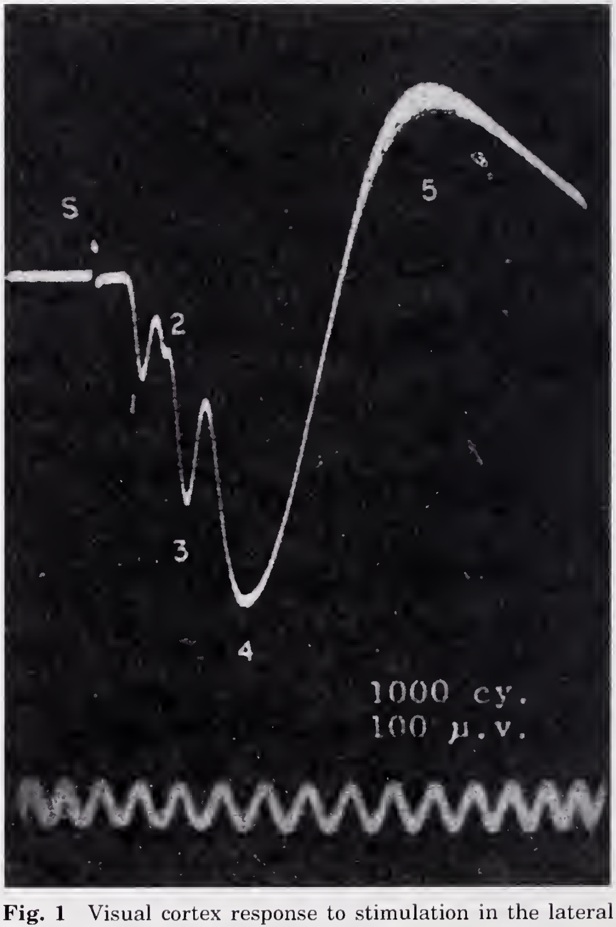


Fig. 1 Visual cortex response to stimulation in the lateral geniculate; ten sweeps at 10-second recurrence rate. The numbers represent the major surface positive (downward) responses of the visual cortex. The authors believed that the third and fourth responses were the cortical response to the incoming afferent volley (3).

Address reprint requests to Professor Peter W. Carmel, Center for Neurological Surgery, New Jersey Medical School, 90 Bergen St., Suite 7300, Newark, NJ 07103.

these animals and recorded action potentials in the motor cortex, whether the portions of the nerve were from muscle or from skin. Another leading physiological group had seen this distribution of sensory potentials and pointed out the need for the study of these potentials after post central ablation. They noted that their "two attempts to make this critical observation acutely and chronically had been unsuccessful" (2). Because of his surgical skills, Malis was able to resect the entire post central gyrus leaving the primary motor cortex intact. The cerebellum was also resected. Malis, Pribram, and Kruger commented that the phenomenon of sensory responses in motor cortex was not accounted for by the known anatomic pathways.

The final paragraph in an article by Malis et al. (1) is so typical that it deserves special mention. He writes that after the paper was submitted he had returned to Mount Sinai and had constructed his own DC amplifiers which had better characteristics than the instruments that he had used at "Mecca." The illustrations that are used here are of the *Sinai experiments* rather than those in New Haven.

Malis and Kruger (3) next turned their attention to the complex action potentials of the visual cortex. Stimulation along the visual pathway either at the level of the optic tract or the lateral geniculate created a complex waveform over the visual cortex (Fig. 1). Malis and Kruger used several methods to attempt to dissect this wave complex. First they measured latency differences for the four surface positive waves of the evoked response when stimuli were applied at different distances from the cortex. They studied the effects on the waveforms of local application of Procaine. The responses were then altered by producing hyperresponses in the first two waves with the use of paired stimuli at various intervals and recurrence rates. Finally, they carefully removed the visual cortex and studied the responses of the exposed white matter. These experiments suggested that the first two surface positive waves represented the arrival of impulses at the cortex from two different fiber groups of the white matter. The third and fourth surface positive waves were felt to represent the cortical response to the arrival of the first and second waves.

Malis was eager to find a method of studying the complex, multilayered geniculate and striate cortex layer by layer. In 1957 he and his coworkers had discovered a method for doing exactly this (4). Malis had struck on the idea of using monoenergetic, heavy ionizing particles to eliminate a single layer in the cortex. This work took advantage of the Bragg peak. This peak occurs when multiple heavy particles, traveling at the same energy, give up their kinetic energy in the form of ionizing radiation over a very limited

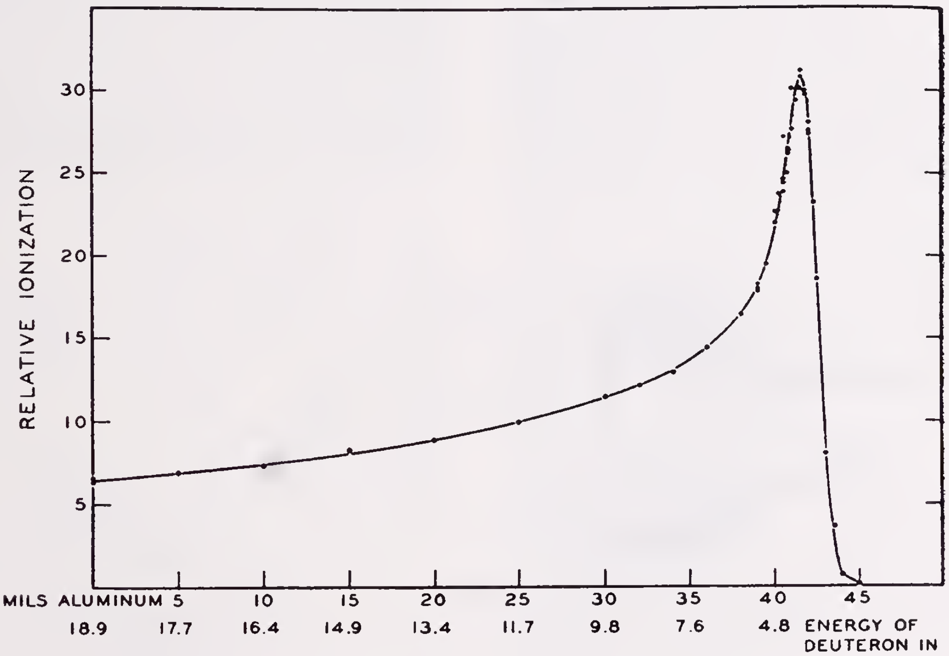


Fig. 2 Typical Bragg Curve: Relative ionization produced by the beam of deuterons. The terminal portion of the curve shows a sharp rise in ionization energy immediately before the monoenergetic particles lost the last of their kinetic energy. If the energies were chosen so that the level of ionization indicated by the arrows killed tissues, the resultant band of destruction would be quite thin (4).

area (Fig. 2). This important work was really the beginning of stereotactic radiosurgery. Tobias and co-workers had used the Bragg peak to irradiate the pituitary gland of the rat (5), but no one had determined how to make small, very precise lesions in the brain using ionizing radiation. In this initial publication, they illustrated a small laminar lesion within the striate cortex, leaving the tissue above and below the level of the lesion unaffected (Fig. 3). This powerful research technique would lead to a series of papers analyzing the striate cortex and its projections, and occupied Malis and his co-workers for the next 8 years.

In 1959 I was starting my last year of medical school and was interested in becoming a neurologist. I had worked on Dr. Morris Bender's Neurology service at Bellevue and started attending his Friday Neurological Grand Rounds at Mount Sinai. These rounds were a genuine free-for-all, in which Leonard Malis was perhaps the smartest, but certainly not the loudest, of all the participants. The only one who ever bested Leonard Malis in these intellectual tumbles was Morris Bender, using his phenomenal memory of the details of the history of every patient he ever saw. Dr. Malis was extremely charismatic, and I decided to spend time in his laboratory.

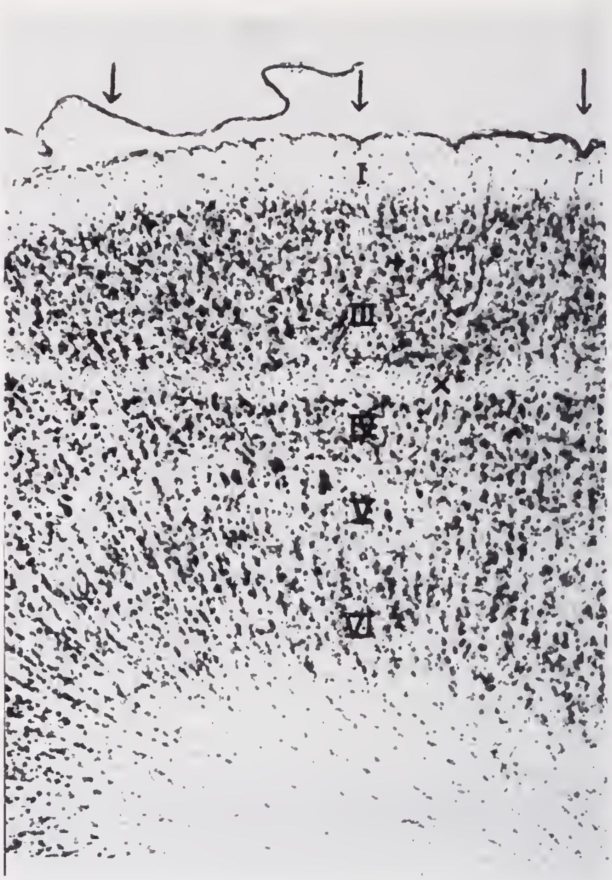


Fig. 3 Cortex of the lateral gyrus of the cat, showing a laminar lesion produced by 10-MeV protons. Arrows indicate the direction of the beam. The cortical layers are indicated by Roman numerals, and the "X" indicates the zone of destruction. This zone has quite sharp borders and there is normal cytoarchitecture above and below this level (4).

This year was occupied with production of laminar lesions, their histological analysis, and microelectrode recordings through the layers of the striate cortex during photic stimulation. It was an exciting, totally absorbing atmosphere, and I worked in the laboratory virtually full-time, in lieu of my fourth year classes. (I had somehow or other forgotten that there was a State Law in New York that required satisfactory completion of the Public Health course for graduation. I was informed approximately 3 weeks before graduation that I would not be getting my M.D. degree. Thanks to an understanding and benevolent

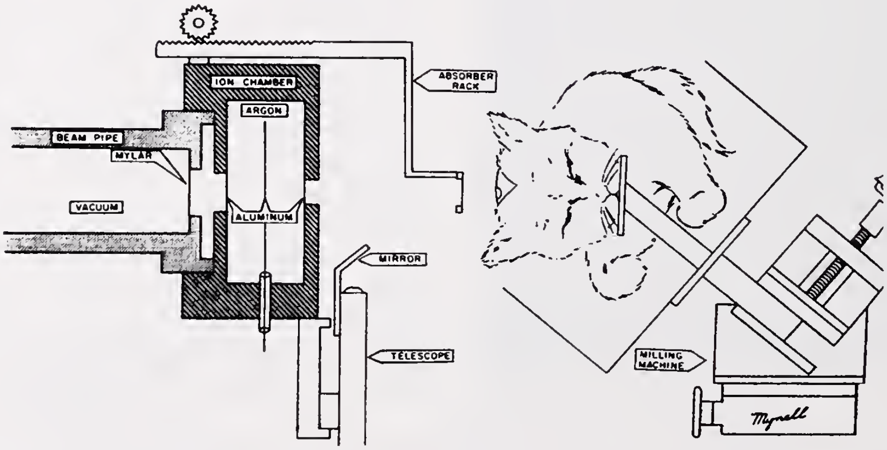


Fig. 4 Scheme of the irradiation setup used to produce laminar lesions in the striate cortex of the cat. The modifications invented by Malis include the telescope with the mirror that allows a precise indication of the site of the lesion. Another modification was the absorber rack where aluminum sheets of varying thicknesses could be added to change the depth of penetration of the beam and the ion chamber to measure the dose.

TABLE 1

The relation of Peak Doses of Irradiation to Histological Findings for 177 Radiation Lesions

Number of Lesions Showing	Relation of Peak Doses (in Thousands of Rads) to Histological Findings					
	<14	15–24	25–34	35–44	45–54	>55
No evidence of lesion	6	1	–	–	–	–
Light laminar lesion	9	16	20	8	–	–
Heavy laminar lesion	–	–	10	25	7	4
Necrotic focus	–	–	2	16	29	24

Source: Malis LI, Baker CP, Kruger L. J Comp Neurol 1960; 115:219–242.

Chairman in Public Health, I was allowed to study for and take the final examination over the course of a weekend, graduating with my classmates.)

After the appearance of the 1957 *Science* paper (4), two papers were published with Charles Baker, who was at the Brookhaven Laboratory, Larry Kruger from the days in John Fulton's laboratory, and Jerzy Rose. Jerzy was the wonderful iconoclastic neuroanatomist who was quick to grasp the importance of the production of the laminar lesions, despite the fact that Jerzy said harsh things about neurosurgeons, including suggesting that the world would be better if all of the neurosurgeons were locked up.

The first of these important papers was on the subject of the technique of lesion production and dosimetry (6). Figure 4 is taken from this paper. It demonstrates how Malis had modified the cyclotron at Brookhaven to produce a more accurate and precise lesion and to assess the direction of the beam field. Several other modifications of the terminal portion of the beam were also Malis inventions to make the beam sharper and more even and to measure accurately the number of particles.

The most important part of this paper is its information on dosimetry. Malis and his coworkers were able to determine the peak doses that caused lesions which were light, heavy, or resulted in a necrotic focus (Table 1). These workers then were able to compare the range of monoenergetic particles in cortex for deuterons, alpha particles, and protons (Table 2). These data were not available anywhere else in the

TABLE 2

Actual and Calculated and Ranges of Deuterons, Alpha Particles, and Protons in Cerebral Cortex of a Rabbit

	Deuterons (20 MV)	Alpha Particles (40 MV)	Protons (10 MV)
Expected range in cortex (μ)	2510	1255	1255
Expected range in cortex (μ) in the experimental set-up	2180	1014	1065
Expected range in mounted tissue (30% less) (μ)	1526	745	710
Actual range in mounted tissue (μ) average (no absorber)	1268 (47)[a]	552 (15)	645 (9)
Range in mounted tissue (μ)			
Aluminum absorber in beam path			
5 mil			
Actual range	1132 (14)	–	–
Expected range	1089		
10 mil			
Actual range	888 (41)	–	–
Expected range	910		
15 mil			
Actual range	730 (12)	–	–
Expected range	731		

[a] The numbers in parentheses indicate the size of the measured samples.

Source: Malis LI, Baker CP, Kruger L. J Comp Neurol 1960; 115:219–242.

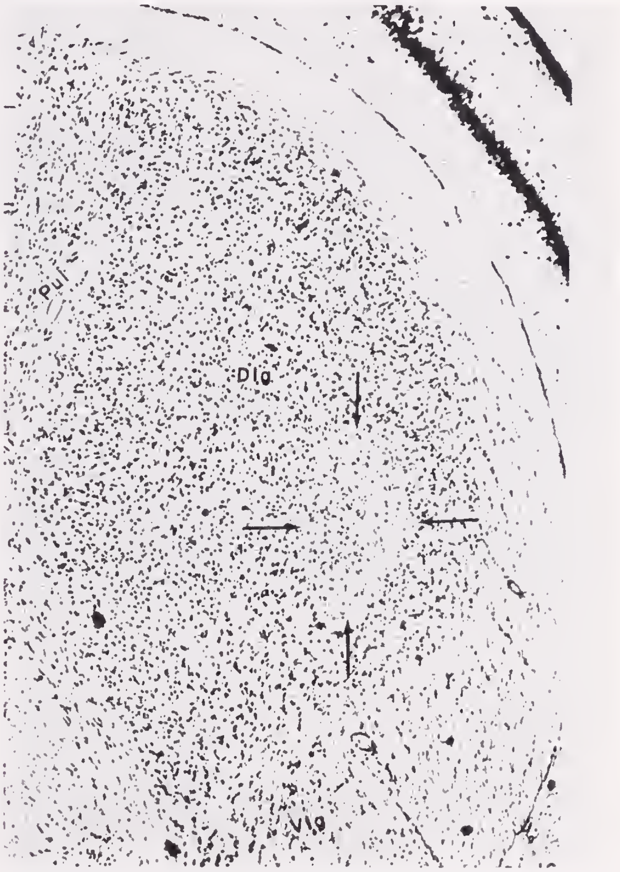


Fig. 5 Section through the dorsal lateral geniculate after a laminar lesion in striate cortex of the cat. The arrows indicate an area of cellular loss as a result of these lesions. This oval area formed a column that ran through the alpha portion of the dorsal lateral geniculate (7). Modified from Rose JE, Malis LI. J Comp Neurol 1965; 125.

world and were a considerable contribution. Jerzy Rose was the first author of the second half of this effort published on the immediately ensuing pages in the *Journal of Comparative Neurology* (7). This paper presented details of the histological changes that followed laminar destruction. Here we see an excellent description and good evidence of axonal sprouting. An abundant growth of fibers crosses the lamina lesions and projects to cortical layers distal to the laminar lesion. This was a particular heresy in 1960 when it was published. At that time there was little or no discussion of regeneration phenomenon, axonal sprouting, reorganization, and plasticity within the nervous system. These concepts owe much of their acceptance to this paper.

The final effort arising from the study of laminar lesions was to document the anatomical connections. Here in two papers with Jerzy Rose the retrograde changes in the geniculate were documented, and the nature of the cyto architectural structure of the dorsal lateral geniculate was identified (8). Of great interest in the latter paper was the finding that a vertical cell column in the striate region receives projections from a cell column which extends throughout the entire thickness of the alpha sector of the dorsal lateral geniculate body (Fig. 5) (9).

Because of the need to be extremely precise in many of the anatomical sections described above, Leonard Malis became an early enthusiast in the use of the operating microscope. He found kindred souls in R.M. Pierdon Donaghy and Gazi Yasargil. These three individuals were the real pioneers in microsurgery as applied to neurosurgery. Leonard Malis' particular contribution was a highly precise bipolar cautery. This instrument made hemostasis in neurosurgery as precise as the microsurgery required.

In 1989 Leonard Malis organized and ran a pioneering neurosurgical microsurgical course. Both Professors Yasargil and Donaghy were on the faculty. This brought microneurosurgery and its techniques to practitioners all over the country.

Mount Sinai finally named Leonard Malis Chairman of Neurosurgery in 1969. Once he was Chairman, he took the opportunity to completely reorganize the neurosurgical laboratories. When the laboratories reopened, Dr. Malis was not at the bench. Instead he was the director of the laboratories giving organization and new ideas to those who were doing the benchwork. He continues to play the role of mentor and friend, which he has always been to me.

References

1. Malis LI, Pribram KH, Kruger L. Action potentials of motor cortex evoked by peripheral nerve stimulation. J Neurophysiol 1953; 16:161–167.
2. Ruch TC, Patton HD, Amassian VE. Topographical and functional determinants of cortical localization patters. Res Publ Assoc Res Nerv Ment Dis 1952; 30:403–429.
3. Malis LI, Kruger L. Multiple response and excitability of cat's visual cortex. J Neurophysiol 1956; 19:172–186.
4. Malis LI, Loevinger R, Kruger L, Rose JE. Production of laminar lesions in the cerebral cortex by heavy ionizing particles. Science 1957; 1266:302–303.
5. Tobias CA, Van Dyke DC, Simpson ME, et al. Irradiation of the pituitary of the rat with high energy deuterons. Am J Roentgenol Radium Ther Nucl Med 1954; 72:1–21.
6. Malis LI, Baker CP, Kruger L. Effects of heavy ionizing monoenergetic particles on the cerebral cortex. I. Production of laminar lesions and dosimetric consideration. J Comp Neurol 1960; 115:219–242.
7. Rose JE, Malis LI, Kruger L, Baker CP. Effects of heavy, ionizing monoenergetic particles on the cerebral cortex. II. Histological appearance of laminar lesions and growth of nerve fibers after laminar destruction. J Comp Neurol 1960; 115:243–296.
8. Rose JE, Malis LI. Geniculo-striate connections in the rabbit. I. Retrograde changes in the dorsal lateral geniculate after destruction of cells in various layers of the striate region. J Comp Neurol 1965; 125:95–120.
9. Rose JE, Malis LI. Geniculo-striate connection in the rabbit. II. Cytoarchitectonic structure of the striate region of the dorsal lateral geniculate; organization of the geniculo-striate projections. J Comp Neurol 1965; 125: 121–140.

Leonard I. Malis and Prophylactic Antibiotics

Sean I. Savitz, B.A.

Abstract

Leonard I. Malis introduced important changes in the antimicrobial regimen for neurosurgical procedures at The Mount Sinai Hospital. Among Dr. Malis' innovations, intraoperative administration of a single dose each of vancomycin and gentamicin or tobramicin and constant irrigation of the surgical site with a bactericidal antibiotic (streptomycin) led to the elimination of primary wound infections during a 20-year period. In a study to locate potential sources of microbial contamination in his operating room, this combination of parenteral antibiotics was justified, because 36% of patients were at risk for exposure to methicillin-resistant *Staphylococcus aureus* and Gram-negative bacteria. Streptomycin as a topical agent was found to be highly efficacious in preventing intraoperative growth of potential pathogens cultured from the surgical wound and the operating room environment. **Key Words:** wound infection, prophylactic antibiotics, topical antibiotics.

Editor's note: When Sean Savitz began his study on the bacteriological factors in clean neurosurgical cases at Mount Sinai in the summer of 1990, he had just graduated from high school. Invited into the operating room to observe a craniotomy and gather culture material, Sean proceeded to contaminate the binocular microscope, the drapes, and even the surgeon's gloves. Dr. Malis assumed that a young researcher in microbiology who had already published two articles in medical journals had the surgical savoir faire of a medical student; he quickly rescrubbed and redraped and never uttered a cross word to his young coauthor.

At The Mount Sinai Hospital, the postoperative administration of antibacterial agents for neurosurgical procedures began in 1925 with the use of the antiseptic, hexamine. As each drug became available, sulfanilimide, penicillin, chloramphenicol, streptomycin, and ampicillin were used sequentially. Patients routinely received antibiotics starting in the recovery room and continued receiving them for 10 days. From 1963 to 1970, all craniotomy and laminectomy wounds were irrigated with bacitracin before closure. During the final 12 months when ampicillin and bacitracin were given, the rate of documented wound infection was 5.1%. When Dr. Malis became head of the neurosurgical service, he introduced the prophylactic use of lincomycin, intraoperatively rather than postoperatively, a change which reduced the infection rate to 2.3%. Statistical analysis revealed that the administration of one preoperative dose of a specific antistaphylococcal agent was equivalent to 40 doses of a broad spectrum of antibiotics given over the first 10 postoperative days (1). Lincomycin was abandoned because of the reported incidence of adverse drug reactions.

In June 1973, to assess the efficacy of antimicrobial prophylaxis in neurosurgery, Dr. Malis approved a prospective, double-blind, randomized study comparing the infection rate following intraoperative clindamycin versus that of a placebo (2). Because of an outbreak of staphylococcal wound infections in the sixth month of the study, he discontinued the investigation, closed the operating room until January 1974, and ordered an analysis of bacterial isolates cultured from wound infections during the previous 5 years. The epidemiologists of the New York City Department of

---

Address reprint requests to Sean I. Savitz, B.A., 55 Old Turnpike Road, No. 101, Nanuet, NY 10954.

Health cultured the personnel, equipment, and supplies. Sham operations were conducted on agar plates using microneurosurgical instruments with the surgical team completely prepped and the microscope and table draped in the usual fashion. No source for the wound infections could be found. At the conclusion of the investigation, the epidemiologists, concerned about bacterial resistance, recommended against the use of prophylactic antibiotics and instead suggested frequent cultures and rapid treatment (3).

After due consideration, Dr. Malis chose a combination of bactericidal antibiotics active against all of the pathogens cultured during the previous 5 years. The antimicrobial regimen consisted of one dose of 80 mg of gentamicin intramuscularly, one dose of 1 g vancomycin intravenously, and constant irrigation of the wound with 50 mg of streptomycin per liter of saline (50 μg/mL). This solution was chosen in an effort to simulate the serum concentration achieved with the usual injected therapeutic dose. He thereby avoided much higher levels that might be attained by intrathecal injection to diminish potential ototoxicity. Based on a review of the literature, constant irrigation with an antibiotic solution represented a novel method of topical prophylaxis. Traditional methods included rinsing, powdering, or spraying the neurosurgical wound just before closure (4).

With this protocol, no instance of postoperative infection was documented in a 5-year study of 1732 cases from the entire Department of Neurosurgery (3). In a published comment at the end of Malis' report, Wright (5) found the data difficult to believe. Subsequent investigations using the "Malis regimen" at other neurosurgical centers recorded that the incidence of postoperative sepsis was lowered to less than 1% (6–9).

The final study (10) of the "Malis regimen" before his retirement assessed potential sources of bacterial contamination in 45 consecutive clean neurosurgical cases. The investigation sought to provide an explanation for the zero infection rate. His regimen of antibiotics was justified by the data that 36% of the operations were at risk for methicillin-resistant staphylococci or Gram-negative species cultured from the patient's skin (5 cases), the surgeon's gloves (1 case), the operating room environment (8 cases), or both the surgeon's gloves and the operating room environment (2 cases). After 1990, when injectable streptomycin became unavailable in the United States because of a Food and Drug Administration decision, Dr. Malis brought his own supply in from Mexico.

In a published comment at the end of the article by Savitz et al. (10), Haines (11) stated that there was a "peculiar disadvantage" in the empirical success of a program of prophylaxis that left no wound infections to analyze. He commented that the results of longitudinal investigation by one group could not substitute for a clinical trial by surgeons who still experienced occasional postoperative sepsis. In letters to the editor concerning subsequent studies on prophylactic antibiotics, Dr. Malis argued that testing of his protocol with placebos or alternations of individual drugs was unacceptable because of the statistically expected wound infections that would occur in his patients (12, 13). He noted that his series reached more than 5000 cases without a primary wound infection during a 20-year period.

The "Malis regimen" described in his seminal article in 1979 (3) established a standard which others should strive to achieve.

References

1. Savitz MH, Malis LI, Meyers BR. Prophylactic antibiotics in neurosurgery. Surg Neurol 1974; 2:95–100.
2. Savitz MH, Malis LI. Prophylactic clindamycin for neurosurgical patients. NY State J Med 1976; 76:64–66.
3. Malis LI. Prevention of neurosurgical infection by intraoperative antibiotics. Neurosurgery 1979; 5:339–343.
4. Haines SJ. Topical antibiotic prophylaxis in neurosurgery. Neurosurgery 1982; 11:250–253.
5. Wright RL. Prevention of neurosurgical infection by intraoperative antibiotics (Comment). Neurosurgery 1979; 5:343.
6. Quartey GRC, Polyzoidis K. Intraoperative antibiotic prophylaxis in neurosurgery: A clinical study. Neurosurgery 1981; 8:669–671.
7. Haines SJ, Goodman ML. Antibiotic prophylaxis of postoperative neurosurgical wound infection. J Neurosurg 1982; 56:103–105.
8. Geraghty J, Feely M. Antibiotic prophylaxis in neurosurgery. A randomized controlled trial. J Neurosurg 1984; 60:724–726.
9. Jannetta PJ. Microvascular decompression of the trigeminal root entry zone. In: Rovit RL, Murali R, Jannetta PJ (eds). Trigeminal neuralgia. Baltimore: William & Wilkins; 1990: 221.
10. Savitz SI, Bottone EJ, Savitz MH, Malis LI. Investigations of the bacteriological factors in clean neurosurgical wounds. Neurosurgery 1994; 34:417–421.
11. Haines SJ. Investigations of the bacteriological factors in clean neurosurgical wounds (Comment). Neurosurgery 1994; 34:421.
12. Savitz MH, Malis, LI. Prophylactic parenteral antibiotics in neurosurgery (Letter). J Neurosurg 1989; 70:150.
13. Savitz MH, Malis, LI. Meta-analysis of antibiotic prophylaxis (Letter). Neurosurgery 1995; 36:1057.

Another Look at Ventriculosubgaleal Shunting Procedures

Martin H. Savitz, M.D.

Abstract

Ventriculosubgaleal shunts were available at the turn of the century as a treatment for hydrocephalus. Almost 80 years later, Perret and Graf advocated such shunting for the temporary decompression of ventricles enlarged by tumors or by hydrocephalus. The use of a subgaleal shunt in acute head trauma was first published in 1983. No direct measurement of intracranial pressure was attempted in 30 cases. Evidence by computed tomography of compressed ventricles and cerebral contusion correlated well with elevated pressure. When the Camino intracranial pressure monitor became available, the device was inserted before placement of the shunt to assess the appropriateness and efficacy of the method in 21 patients. An additional 22 cases of intraventricular hemorrhage with acute hydrocephalus were treated over a 17-year period. The simple method of shunting into the subgaleal space has broad application for the temporary relief of increased intracranial pressure or high-pressure hydrocephalus. **Key Words:** closed head injury, Cushing's triad, intracranial pressure, cerebral contusion, hydrocephalus.

Editor's note: Dr. Malis used ventriculosubgaleal shunts primarily to relieve hydrocephalus in patients awaiting posterior fossa craniectomy or craniotomy for removal of tumors; temporary decompression rather than ventriculoperitoneal shunting prevented postoperative hemorrhage and dependence on a permanent implant. Before beginning to use ventriculosubgaleal shunting in my suburban practice, Dr. Malis told me that he had learned the technique more than 10 years earlier from Professor Jan-Michel Gybels in Belgium.

Ventricular tap for measurement and relief of intracranial hypertension was available in the latter part of the 19th century; removal of small amounts of cerebrospinal fluid from the cranial cavity could lower high pressure to normal range (1). In 1929, Davidoff (2) reviewed ventriculosubgaleal shunting as a treatment for hydrocephalus. Almost five decades later, Perret and Graf (3) advocated such shunting by a parietal approach for the temporary decompression of ventricles enlarged by tumors and by hydrocephalus. An additional series was performed by a frontal approach by Drabkin et al. (4) in 1980; a finite period of ventricular decompression allowed resolution of the primary cause of hypertensive hydrocephalus or adequate time for diagnosis and surgical excision of a tumor.

The use of ventriculosubgaleal shunting in acute head trauma was first reported to the New York Society of Neurosurgery in 1981 (5). No direct measurement of intracranial pressure was attempted in 30 cases (6) of severe closed head injury (Grade III or IV) treated during a 10-year period (Table 1). Evidence by computed tomography (CT) of compressed ventricles (Fig. 1) and cerebral contusion (Fig. 2) correlated well with elevated pressure (7). When the Camino intracranial pressure monitor became available at two

---

From the Division of Neurosurgery, Department of Surgery, Nyack Hospital and Good Samaritan Hospital, Rockland County, New York. Address reprint requests to Martin H. Savitz, MD, 55 Old Turnpike Road, No. 101, Nanuet, NY 10954.

TABLE 1
Prior Cases Without ICP Monitoring

	No.	Expired	Rehab[a] center	Home
Grade III	24	1	18	5
Grade IV	6	6	–	–

[a] Rehab, rehabilitation

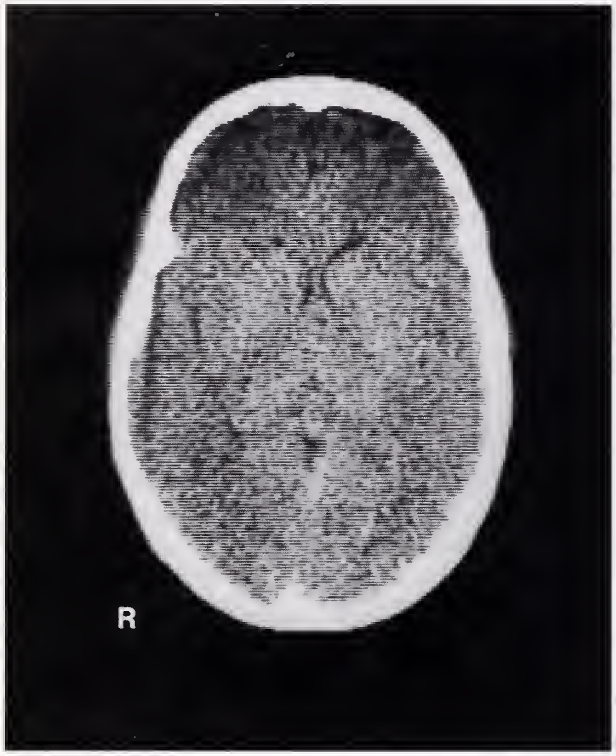


Fig. 1. CT scan of head showing narrowing of ventricular system consistent with diffuse cerebral edema.

community hospitals, the device (Fig. 3) was inserted before placement of the shunt (Fig. 4) to assess the appropriateness and efficacy of the method (8).

Methods and Materials

Twenty-one cases (Table 2) of severe head trauma (Glascow coma scale 3–5) with CT evidence of cerebral contusion and edema manifested signs of increased intracranial pressure and brainstem compression. Cushing's triad was recorded in each case: bradycardia, bradypnea, and hypertension. There were no focal findings on neurological examination and no vault fractures on skull x-rays. Dexamethasone (100 mg) and mannitol 20% (500 cc) were given intravenously in the emergency room. Immediate intubation facilitated hyperventilation, and further evaluation was carried out by CT. The Camino OLM Kit provided all the necessary instruments and accessory items to be used in combination with the Camino 420 Digital Pressure Monitor (Camino Laboratories, San Diego, CA).

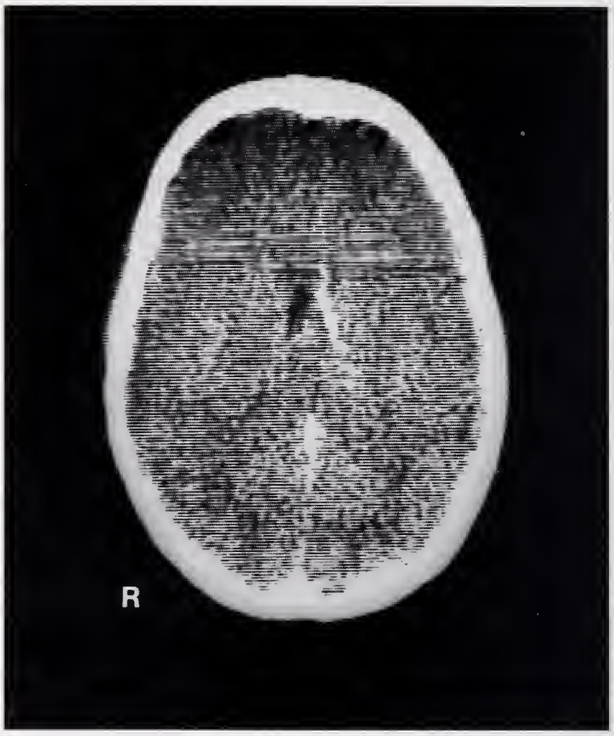


Fig. 2. CT scan without contrast. Note blood in relation to left lateral ventricle.

The small ventricles were tapped by a right frontal approach 11 cm from the nasion and 3 cm to the right of the midline. A Pudenz ventricular catheter was inserted; the cerebrospinal fluid obtained under pressure was 10 to 20 cc in volume and grossly hemorrhagic. About 4 cm of tubing was tucked into an 8-cm pocket created above the periosteum by dissecting the loose areolar subgaleal tissue with a hemostat. Accurate two-layer closure of the galea and skin was performed with fine sutures.

During the 17 years, 22 cases of intraventricular hemorrhage with acute hydrocephalus were treated by temporary parietal subgaleal shunts. Control of hypertension by appropriate medication was an integral part of the therapy. The 50% who survived required permanent shunting even though the dilation of the ventricles resolved. The same burr hole was available for placement of the proximal end of the shunt tubing.

Results

In the cases of acute head trauma, the subgaleal collection of fluid lasted 3 to 5 days, the period of brain swelling. The reduction in intracranial pressure was evident by immediate im-

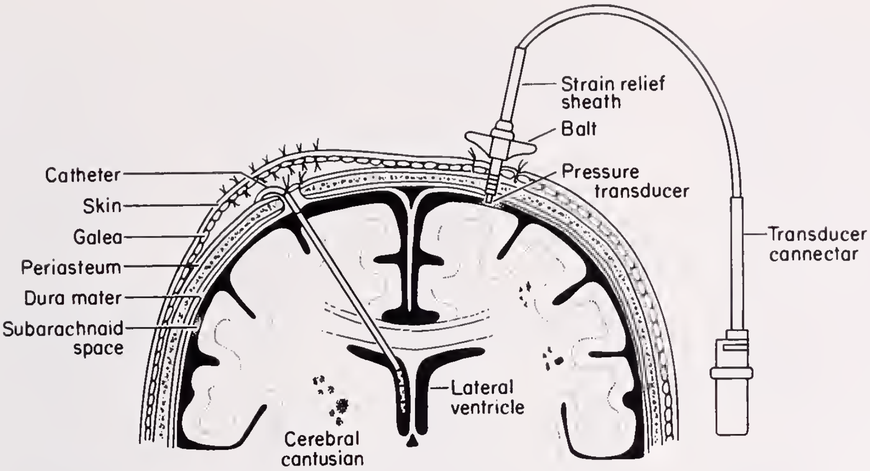


Fig. 3. Artist's illustration of insertion of Camino ICP monitor into left frontal area and Pudenz catheter into right lateral ventricle.

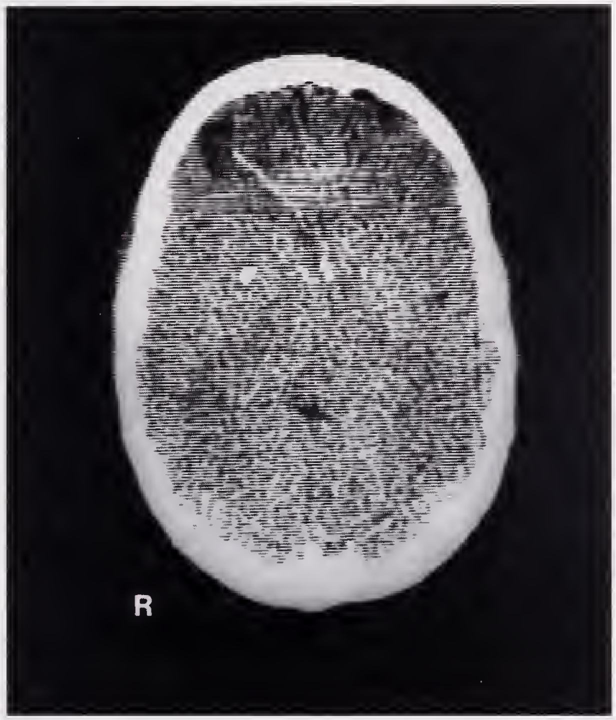


Fig. 4. Catheter is properly positioned. Note small high-density foci representing areas of cerebral contusion.

provement in neurological status: hyperventilation, hypertension, and hyperthermia resolved. Follow-up CT scans were unremarkable (Fig. 5). Significant recoveries were observed in the surviving patients who had been monitored, and the shunts were removed without complications after 7 days. One monitored patient regained normal cortical function during her hospitalization for multiple trauma. After 2 to 6 months of rehabilitation and occupational therapy, 14 patients were discharged home in the care of their families. Six patients whose condition deteriorated rapidly in the emergency room to fixed dilated pupils and no reflexes or spontaneous respiration did not reverse their coma and met brain death criteria within 72 hours; follow-up CT scans showed areas of hemorrhagic infarction (Fig. 6). rather than resolution and absorption. Nine patients with basilar skull fractures ceased leaking cerebrospinal fluid after shunting.

The results in the first 30 patients shunted without an intracranial pressure (ICP) monitor (Table 1) were quite similar. Six patients categorized as grade IV (no evidence of brain function) in the emergency room did not improve and died within 72 hours. The remaining patients categorized as grade III (no eye opening, no verbal response, motor response limited to abnormal flexion or extension) transferred to a rehabilitation center with the exception of a 16-year-old boy who suffered a fatal pulmonary embolus on his 30th postoperative day.

In the 22 cases of acute hydrocephalus caused by intraventricular hemorrhage, the subgaleal collection continued. During the acute phase of neurosurgical treatment, the shorter catheter had less incidence of clogging and could be easily removed before insertion of a ventriculoperitoneal shunt. The 50% who survived made neurological recoveries ranging from vegetative to functional states.

Discussion

The prior neurosurgical literature on subgaleal shunts is quite limited (2–4). Open ventriculostomy carries a major risk of infection, whereas ventriculosubgaleal shunting has the advantage of being a truly closed system. The absorptive capacity of the subgaleal space has been well documented (2–4). Inasmuch as high-pressure hydrocephalus was controlled for periods of 3 weeks up

TABLE 2
Patient Characteristics with ICP Monitoring

Sex	Age (yr)	Glascow Coma Scale	Complications	Initial ICP	Postshunt ICP	Tracheostomy Gastrostomy	Outcome
F	23	4	otorrhea	26	2–5	no	home
M	19	4		31	3–10	no	rehab center[a]
M	32	3		24	3–10	yes	expired(72 h)
M	19	5	otorrhea	26	0–7	yes	rehab center
M	40	3		31	0–4	no	rehab center
F	44	5		26	0–8	yes	rehab center
F	16	4		20	2–10	no	rehab center
M	16	5	rhinorrhea	22	0–8	no	rehab center
F	15	3	rhinorrhea	82[b]	6–18[c]	yes	expired(72 h)
F	29	3	otorrhea	52	2–10	no	expired(72 h)
M	69	5		42	3–10	yes	rehab center
M	50	5		21	0–6	no	rehab center
M	27	5	otorrhea	21	0–8	yes	rehab center
M	22	3	otorrhea	80[b]	8–19[c]	no	expired(72 h)
F	31	5		24	0–6	no	rehab center
M	19	5		27	0–7	no	rehab center
F	40	4		62	2–10	no	expired(72 h)
F	60	5	otorrhea	34	5–10	no	rehab center
M	36	4		30	11–20[c]	yes	expired(72 h)
M	41	4		53	0–8	no	rehab center
M	46	4	otorrhea	86	2–8	yes	rehab center

[a] Rehab center, rehabilitation center.
[b] Insertion delayed because of coagulopathy.
[c] Required additional mannitol.

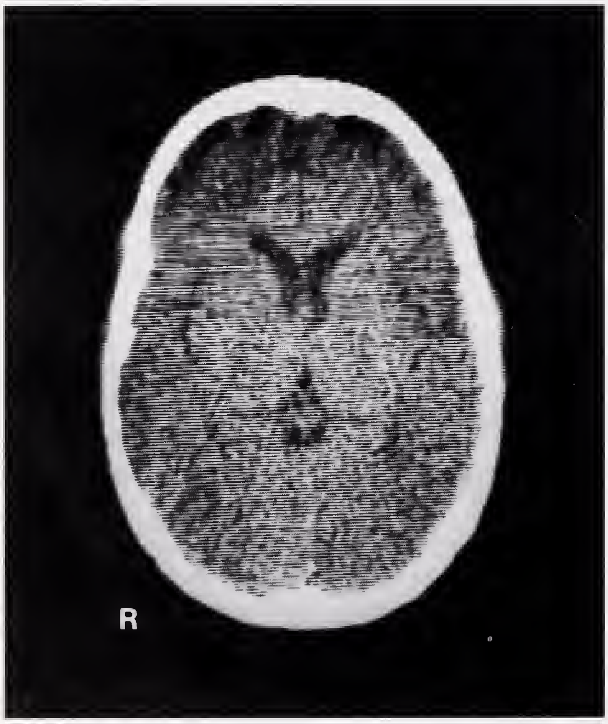


Fig. 5. Ventricles have returned to normal size and configuration. Note resolution of contusion.

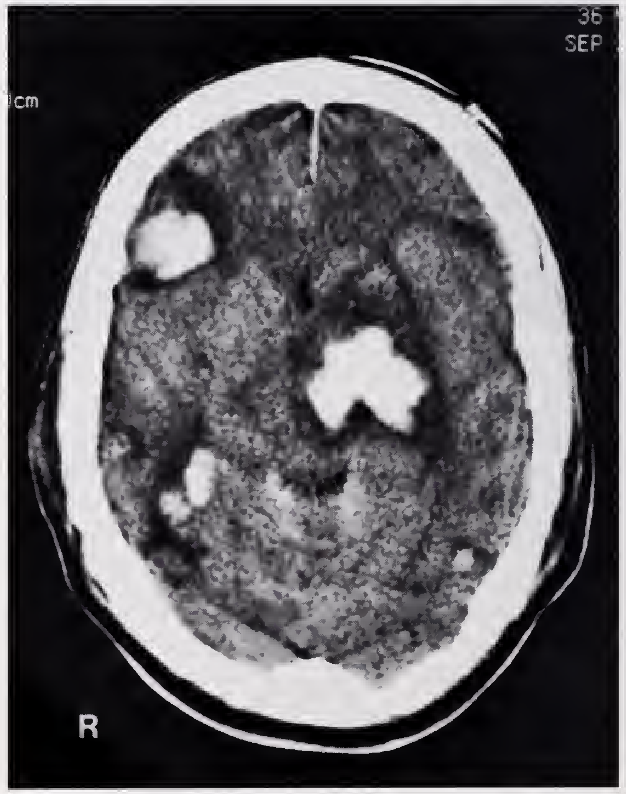


Fig. 6. Areas of diffuse contusion have coalesced into multiple intracerebral hematomas.

to several months, the membranes of the scalp contributed to handling high volume and reducing cerebrospinal fluid pressure to normal range. The simple method of shunting into the subgaleal space has broad application for the temporary relief of increased intracranial pressure in acute head trauma or high-pressure hydrocephalus.

Acknowledgments

The author wishes to express his thanks to Mr. Michael Carlin and Mrs. Harmony Savitz who prepared the illustrations for publication.

References

1. Venes JJ. Intracranial pressure monitoring in perspective. Childs Brain 1980; 7:236–240.
2. Davidoff LM. Treatment of hydrocephalus: historical review and description of a new method. Arch Surg 1929; 18:1737–1742.
3. Perret GE, Graf CJ. Subgaleal shunt for temporary ventricle decompression and subdural drainage. J Neurosurg 1977; 47:590–594.
4. Drabkin AJ, Levine ME, Yang WC. Ventriculo-subgaleal shunt: Evaluation by computed tomography. Acta Neurochir (Wein) 1980; 55:107–110.
5. Savitz MH, Katz SS. Ventriculoperitoneal shunting for acute head trauma. Crit Care Med 1983; 11:290–293.
6. Savitz MH. Ventriculosubgaleal shunting for acute head trauma. 10 years' experience. J Neurol Orthop Med Surg 1991; 12:205–208.
7. Tabaddor K, Danziger A, Wisoff HS. Estimation of intracranial pressure by CT closed head trauma. Surg Neurol 1982; 18:212–215.
8. Savitz MH. ICP monitoring of subgaleal shunting for acute head trauma. J Neurol Orthop Med Surg, in press.

Neuroradiology at The Mount Sinai Hospital

YUN PENG HUANG, M.D.

Editors note: Dr. Huang was a quiet, distinguished, sagacious professor during my neurosurgical residency at Mount Sinai. His conferences required hours of preparation for the single scheduled hour of meeting with Dr. Malis and the entire Department of Neurosurgery. Getting all of the films from myelograms and angiograms performed every week meant putting hundreds of x-ray images in order on dozens of automated individual viewing boxes. Each resident assigned to a rotation in neuroradiology soon found that Dr. Huang arrived at the hospital earlier and left later than most of the doctors on the neurosurgical service. Over the years, he always found time to personally review neuroradiologic studies with every attending neurologist and neurosurgeon. When Dr. Malis supervised the building of his own operating rooms, color monitors were set up not only for resident instruction but for immediate review and discussion by two-way coaxial cable links with Dr. Huang at his own desk in neuroradiology. Dr. Huang completed his neurosurgical residency at Mount Sinai and then made the change to neuroradiology. He rose to international preeminence in neuroradiology, and he trained an entire generation of Mount Sinai neurosurgeons as well as Fellows who came to him from all over the world. He retired as Professor of Radiology in June 1996 and is now hard at work completing another textbook.

I AM WRITING WITH NOSTALGIA of the happy and fruitful 40 years of association with Dr. Leonard Malis from 1956 to 1996. His contributions to neuroradiology were not many, but were of high quality and even outstanding. His study of the Arnold Chiari malformation (1) clearly outlined the embryology and pathophysiology. The report on compression of the spinal cord and cauda equina in achondroplastic dwarfs (2) began the modern understanding of spinal stenosis. The subject of lumbar narrow canal syndrome was more fully treated in a later publication (3). The concept of the sagittal diameter of the bony cervical spinal canal and its significance in cervical spondylosis was presented at the New York Society for Neurosurgery in 1951. Dr. Leo Davidoff, then Chairman of Neurosurgery at Mount Sinai, was vehemently opposed to the concept of cervical stenosis and refused to allow Dr. Malis to publish. The data appeared in a 1956 paper (4) submitted from the Department of Radiology with its chairman, Dr. Bernard Wolf, as the senior author. In 1994, the original manuscript was updated and published in a special issue of this journal (5) on current controversies in cervical disc disease.

Until Lipiodol, a thick oily compound, was replaced by Pantopaque as the contrast medium, definitive myelographic studies were not possible. Throughout the World War II era, the armed forces had a virtual monopoly on the use of Pantopaque and dictated 3 cc of contrast material per study confined to the lumbar area. Dr. Malis' description of the full column technique (6) allowed adequate imaging of lumbar and thoracic lesions. With larger quantities of Pantopaque injected into the spinal canal, moving the dye into the cervical area became possible with a tilt table and fluoroscopic control (7). The biplane fluoroscopic unit installed at The Mount Sinai Hospital in 1961 was invented by Dr. Malis and became the fore-

---

Address reprint requests to Yun Peng Huang, M.D., 6 Lynn Drive, Englewood Cliffs, NJ 07632.

runner of all lateral fluoroscopic units in the world until the advent of image intensifiers.

His knowledge of the mechanical and electronic aspects of medical science were even more astonishing. He was able to fill in the values of components appearing on brand new electronic diagrams within 20% of error if the numbers were erased and the deficient diagrams were handed to him. Dr. Malis built an automatic cassette changer for cerebral angiography in the basement of his home in 1952. Seven cassettes were held in the changer and each triggered the succeeding x-ray exposure at 1-second intervals. The angiographic images were crisp and as sharp as plain skull films taken individually with a grid cassette. By the time he published his report (8) in 1957, more than 50,000 film exposures had been made; and the machine tolerated daily use for another 6 years.

I met Dr. Malis in 1956 when I began my residency training in neurosurgery; he was the youngest member of the neurosurgical attending staff. We learned neuroradiology together, setting long lines of films in front of rows of bare fluorescent bulbs strung the length of his unfinished, unheated attic, working in overcoats through the long nights whenever we were scheduled to be off duty beginning a warm friendship that has been a mutual pleasure. After my residency I spent a year with Norman Dott at the Edinburgh Royal Infirmary and then a year in Dr. Malis' research laboratory.

The section of Neuroradiology at Mount Sinai School of Medicine grew out of the Department of Radiology. Dr. Wolf, then chairman of the Department of Radiology, recognizing how completely specialized neuroradiology had become, asked Dr. Malis to make neuroradiology part of the Department of Neurosurgery. Dr. Malis instead asked that Neuroradiology be recognized as a separate department.

I then began my studies of the vascular anatomy of the posterior fossa using perserved normal brains. In one set of specimens, catheters were inserted into the jugular veins or dural sinuses. A barium-gelatin mix or lead oxide-resin mix was then injected. In another set, the basilar artery was cannulated and injected with the contrast medium solution. Brain slices of 8 to 10 mm in thickness were then x-rayed and reconstructed in stereoscopic pairs to provide three-dimensional viewing (9). I had been exposed to the concept of stereoscopic viewing of pneumoencephalography by Dr. Benno Schlesinger, a world class neuroanatomist, who had described the blood supply of the thalamus and basal ganglia. (Dr. Schlesinger was Associate Attending Neurosurgeon at Mount Sinai at that time.) In 1958, I began further training at the Edinburgh Royal Infirmary, where all cerebral angiography was taken in stereo pairs by means of hand-pulled cassettes. After returning from Scotland, I asked Dr. Malis to create a stereoscopic cerebral angiographic unit. Shifting a single x-ray tube back and forth the required distance once per second was not feasible, and two tubes were too wide to permit the correct side-by-side placement at the practical distance from the patient, which was limited by the power of the x-ray tubes then available. By placing the two tubes with one slightly closer to the patient, he was able to obtain the correct lateral spacing. Although right and left images differed in size, the 7% difference was within the limit of visual fusion. By setting his cassette changer to fire these tubes sequentially, he was able to obtain stereo pairs with converging central x-ray beams. In addition to the great advance in clinical diagnostic accuracy, review of each complete set permitted identification of the exact anatomic course of the supratentorial and infratentorial vasculature. Superimposing and tracing the arterial and venous phases allowed correlation with the laboratory anatomical injection studies at Mount Sinai and total conceptualization of the cerebrovascular system.

As an example of his forethought, in 1969, reading in an electronic engineering newspaper, he encountered a description of an experimental device designed to pass columnated x-ray beams in a series of laterally shifted radial projections, with computer calculation of the densities at each crossing point. This was printed out as a grid of numbers, as a sort of map of the scanned slice. Dr. Malis raced into Dr. Wolf's office, insisting that they should at once travel to England to the EMI Record Company to meet with Godfrey Hounsfield, the inventing engineer, so that Mount Sinai could pioneer in the development of this device. Dr. Wolf politely threw him out. In 1975 Mount Sinai acquired its first computed tomography (CT) scanner, by then one of the commercially available clinical machines. In 1975 when Dr. Malis was a session chairman of the International Congress of Neuroradiology, in his concluding statement he noted that no papers on CT scanning had been presented and predicted that such papers would predominate at the next Congress, a prediction which was fulfilled. It was not until 1981 in Stockholm, when Mr. Hounsfield received the Nobel prize, that Dr. Malis finally met him.

At the beginning of the CT era, governmental regulation restricted the use of CT scanning to cranial scanning. The need for spinal imaging was obvious. With Dr. Hiroshi Nakagawa, a graduate of the neurosurgical residency at Mount Sinai as senior author, we published basic papers on spinal CT scanning (10, 11). Dr. Nakagawa is now professor and chairman of neurosurgery at Aichi Medical University in Nagoya, Japan.

The specialty of neuroradiology owes a debt of gratitude to Leonard Malis for his past guidance and enlightenment, abundance of fresh ideas, understanding of the role of imaging in neurological diagnosis, realization of the importance of neuroradiology in neurosurgical patient care, and ceaseless uncompromised support. With this happy occasion, the following work with Dr. Toshio Okudera, Dakio Fukusumi, Dr. F. Maehara, Dr. A.L. Stollman, and Dr. Harold A. Mitty will be dedicated to our mentor, Dr. Malis.

References

1. Malis LI, Cohen I, Gross SW. Arnold Chiari malformation. Arch Surg 1951; 63:783–798.
2. Epstein JA, Malis LI. Compression of spinal cord and cauda equine in achondroplastic dwarfs. Neurology 1955; 5:875–881.
3. Malis LI. Lumbar stenosis. Mt Sinai J Med 1991; 58:121–124.
4. Wolf BS, Khilnani M, Malis LI. The sagittal diameter of the bony cervical spinal canal and its significance in cervical spondylosis. J Mt Sinai Hosp 1957; 24:54–61.
5. Malis LI. Cervical spinal cord compression and anteroposterior diameter. Mt Sinai J Med 1994; 61:218–223.
6. Malis LI, Newman C, Wolf BS. Full column technique of lumbar myelography. Radiology 1953; 60:18–28.
7. Malis LI. The myelographic examination of the foramen magnum. Radiology 1958; 70:196–221.
8. Malis LI. An automated cassette changer for cerebral angiography. J Mt Sinai Hosp 1957; 24:54–61.
9. Salamon G, Huang YP. Radiologic anatomy of the brain. New York: Springer-Verlag; 1976.
10. Nakagawa H, Huang YP, Malis LI, Wolf BS. Computed tomography of intraspinal and paraspinal neoplasms. J Comput Tomog 1977; 1:377–390.
11. Nakagawa H, Malis LI, Huang YP. Computed tomography of soft tissue masses related to the spinal column. In: Post MJD, ed. Radiographic evaluation of the spine. New York: Masson Publishing; 1980:320–352.

Venous Architecture of Cerebral Hemispheric White Matter and Comments on Pathogenesis of Medullary Venous and Other Cerebral Vascular Malformations

YUN PENG HUANG, M.D.,* TOSHIO OKUDERA, M.D.,‡ AKIO FUKUSUMI, M.D.,§ FUMIAKI MAEHARA, M.D.,¶
ARYEH L. STOLLMAN, M.D.,* ROGER MOSESSON, M.D.,* MIKE LIDOV,* AND HAROLD A. MITTY, M.D.*

Abstract

The parenchymal veins, especially the deep medullary veins, of the cerebral hemispheres were studied in detail by analyzing the stereoroentgenograms of multiple brain slices of postmortem injected brain specimens (injected into the internal carotid arteries in 17 cases and into the jugular veins in 12 cases). The presence of four zones—the first (or outer), the second (or candelabra), the third (or palmate) and the fourth (or subependymal) zone—of venous convergence was confirmed within the centrum semiovale, particularly in the frontoparietal area. Other venous convergences such as those related to the optic radiation in the para-atrial area were also found. Arterial branching zones were also observed in the areas similar to those of the medullary veins. It appears that these converging zones are created by rapidly growing crossing nerve fiber tracts, i.e., projection, commissural, and association fibers which grow rapidly during intrauterine and postnatal life. Pathogenesis of medullary venous malformation is also discussed from anatomical viewpoint, venoarchitecture of the pial, parenchymal, and subependymal veins and of the dural venous sinuses. The possibility of a similar mechanism (partial, mild, repetitive venoocclusive disease developing over a long period with fluctuating venous pressure) leading to formation of most (if not all) cases of medullary venous malformation and in some, if not many, cases of cerebral vascular malformations [aside from gene abnormality (chromosome 7) in familial cavernous angiomatosis, particularly in Hispanic American or other familial hereditary conditions] has been postulated. **Key Words:** vascular architecture, white matter, cerebral hemisphere, radiologic anatomy, vascular malformation, pathogenesis.

THE PARENCHYMAL VEINS of the cerebral hemisphere have been divided into those that drain superficially and those that drain deeply (1). Those that drain superficially include the intracortical, subcortical, and superficial medullary veins, whereas those that drain deeply are the deep medullary veins and form four zones of venous convergence on their way toward the superolateral corner of the lateral ventricle (2). The purpose of this presentation is to describe these four converging zones and their derivation, the knowledge of which was obtained from 12 adult "normal" brains injected with gelatin-mixed barium sulfate using a catheter inserted into an internal jugular vein or veins (12 brains). These will be

---

From *Mount Sinai School of Medicine, Department of Radiology, New York, NY 10029; ‡Akita Research Institute of Brain and Blood Vessels, Department of Radiology, Akita City, Akita 010 Japan; §Nara Medical College Hospital, Department of Radiology, Kashihara City, Nara 634 Japan; ¶Hitoyoshi General Hospital, Hitoyoshi City, Kumamoto 868 Japan. Address reprint requests to Yun Peng Huang, M.D., 6 Lynn Drive, Englewood Cliffs, NJ 07632.

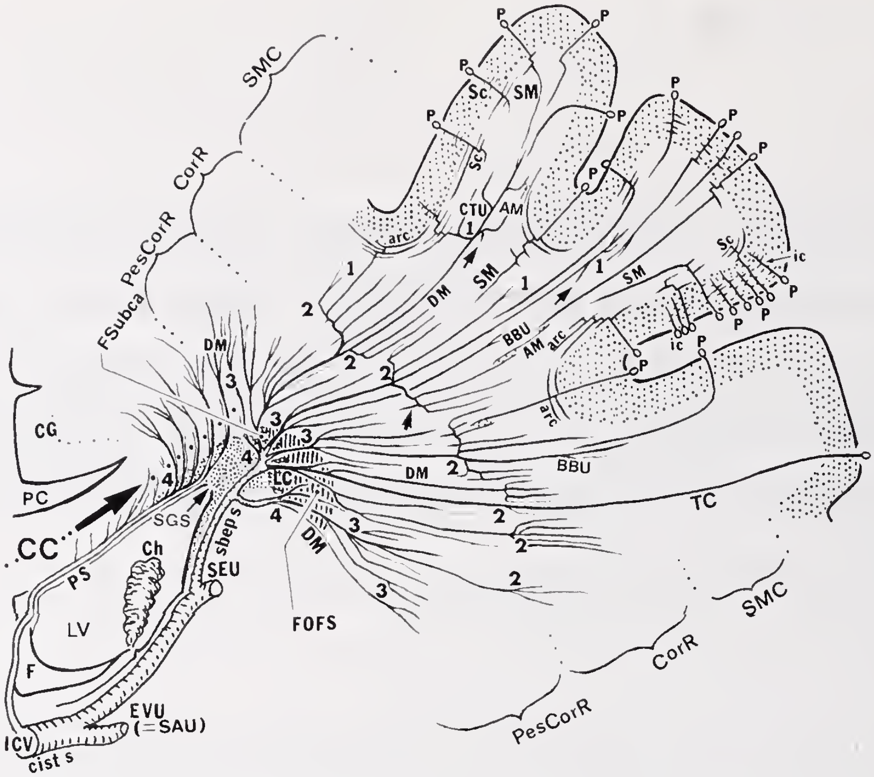


Fig. 1 Schematic diagram showing parenchymal veins in the coronal plane in the frontoparietal area. Labels: AM, anastomotic medullary vein; arc, arcuate veins; BBU, bamboo-branch union; Ch, choroid plexus; CG, cingulate gyrus; cists s, cisternal segment; subep s, subependymal segment of a subependymal vein; CorR, corona radiata; CTU, the coat-tree (or hat-tree) union; DM, deep medullary veins; Cist U, cisternal union; SAU, subarachnoid union; F, fornix; FOFS, superior occipitofrontal fasciculus; F subca, subcallosal fasiculus; ic, intracortical vein; ICV, internal cerebral vein; LC, longitudinal caudate vein; LV, lateral ventricle; P, pial vein; Pes CorR, foot of the corona radiata; PS, posterior septal vein; Sc, subcortical vein; SEU, subependymal union; SM, superficial medullary vein; SMC, substantia medullaris cerebri; TC, transcerebral vein. **1** is the first (or outer) zone of convergence; **2** is the second (or candelabra) zone of convergence; **3** is the third (or palmate) zone of convergence; **4** is the fourth (or subependymal) zone of convergence. CC is the corpus callosum and the large arrow is its radiation. The smaller arrow points to an upside-down tributary of a deep medullary or gyral medullary vein. The deep medullary veins have the first (or outer), second (or candelabra), third (or palmate), and fourth (or subependymal) zone of convergence. Seen in the outer part of the centrum semiovale are the veins with CTU within the gyral white matter and with BBU, although atypical forms of these unions can be found in other zones. The second, third, and fourth zones of venous convergence appear to be related, respectively, to the junction between the CorR and the PesCorR, between the PesCorR and the SRCR complex and between the latter and the subependymal glial substance. The SRCR includes in its most (medial) part, the F subca-FOFS. The fourth (or subependymal) zone of convergence, as stated above, occupies the outer portion of the subependymal glial substance (SGS, dotted area) which caps the superior lateral corner of the LV. Situated in the fourth (or subependymal) zone of the convergence is the longitudinal caudate vein of Schlesinger (LC) and the anterior caudate tributary of the thalamostriate vein. They rightly belong to the subependymal venous system. Separation, elongation, and slenderization of the parenchymal veins are also evident in the area where callosal fibers extend outward (largest arrow and line of large dots). Subcortical veins, in receiving arcuate veins, frequently take a zig-zag course at the level of arcuate fibers. Superficial medullary veins on or near the convex side are usually prominent and long and usually do not take a zig-zag course in penetrating the arcuate fibers.

compared with zones of arterial branching in similar locations using 17 injected adult brains obtained in the postmortem room. The brain slices were made in 8- to 10-mm thicknesses and their roentgenograms were taken in stereoscopic pairs. Analysis of our collected material of medullary venous malformations and other cerebral vascular malformations were also the basis of our investigation (2, 3). Comments on pathogenesis of medullary venous and other cerebral vascular

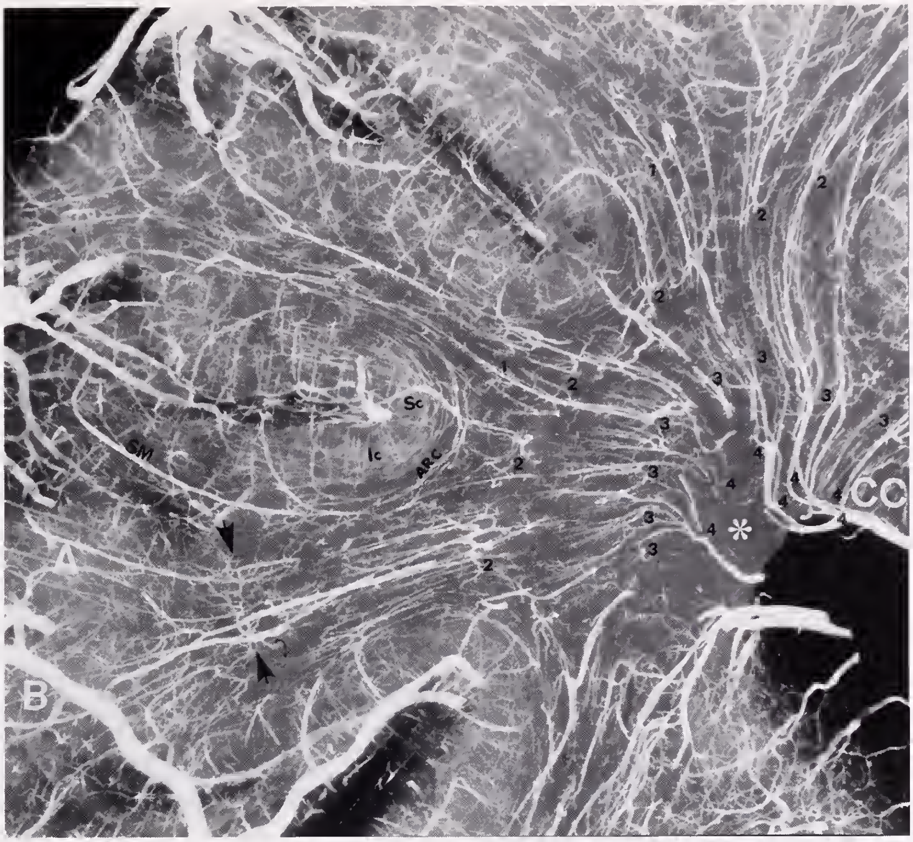


Fig. 2 Roentgenogram of coronal slice of an injected brain showing the first (1), second (2), third (3), and fourth (4) zones of convergence. Labels: ARC, arcuate veins; CC, corpus callosum; Sc, subcortical veins; SM, superficial medullary; Ic, intracortical veins. The asterisk (*) indicates the location of subependymal glial substance which is the slough site of the germinal matrix (in forming the cortex through migration of neuroblasts in early fetal life). Note that prominent superficial medullary veins (SM) usually join a pial vein in the outer portion of sulci (or the convex side of the gyri), whereas those that drain into a pial vein in the depth of sulci (usually subcortical vein) are short and frequently associated with a prominent arcuate vein or veins (ARC). Pseudocandelabra veins (opposing black arrows) are related to a prominent bifid gyrus (A and B) with the in-between cortex projecting and compressing the medullary veins inward, thus creating an apparent second candelabra zone superficial to the normal candelabra veins, although occasionally there maybe true atypical candelabra veins in these areas.

malformations will also be made from the viewpoint of venoarchitectures of the cerebral hemispheres and their covering, including dural venous sinuses.

Results

Typically the deep medullary veins in the frontoparietal area converge in four zones as they traverse the cerebral white matter deeply to join the subependymal venous system (Figs. 1 and 3). The most prominent converging zone is the second or "Candelabra" zone of convergence which is most conspicious in the frontoparietal area and is located in the outer one third zone of the centrum semiovale. In the injected specimens, this is best demonstrated in coronal slices. At this level, smaller and shorter deep-running medullary veins are connected transversely to the main venous stems coming from the first (or outer) converging zone (to be described below) by side tributaries appearing similar to a row of branching candelabra (Figs. 1 and 2). After union, the combined venous trunks of each candelabrum continue inferomedially toward the superolateral corner of the lateral ventricle to form the third (or palmate) zone of convergence at approximately the inner one third zone of the centrum semiovale. The mode of union is palm-like. Fine short medullary veins which originate from the region at or below the level of the candelabra also converge and join the main stem of each candelabrum at this level. The combined deep venous trunks continue inferomedially and unite with other similar trunks to form the fourth (or sub-

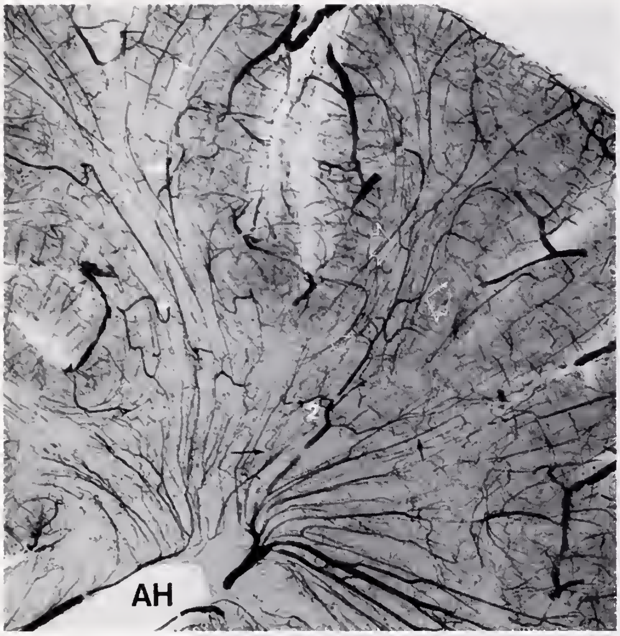


Fig. 3 Bamboo-branch and hat-tree (or coat-rack) unions. Roentgenogram of an injected coronal brain slice showing left posterior frontal area above the anterior horn (AH). Seen above the candelabra zone of convergence are types of venous convergence: hat-tree (or coat-rack) union (empty arrow) which may be incomplete (medial upper empty arrow); bamboo-branch union (solid arrowheads). Atypical forms of these two types of unions are observed in other zones of convergence (black arrow), however.

ependymal) zone of convergence. The first (or outer) zone of convergence spreads over the outer part of the centrum semiovale (mostly bamboo branch union) or is located in the white matter of cerebral gyri (hat-tree or coat-tree union) (Fig. 2). It should be added that incomplete forms of unions can be seen anywhere within the hemispheric white matter.

These modes of union with four zones of convergence are best exemplified in the frontoparietal area; however, the streaming pattern of the deep medullary veins in the lateral atrial area (near the trigon) is somewhat dissimilar where three zones of venous convergence are noted, namely the outer and inner sagittal and the subependymal zones of convergence (see below) (Figs. 4 through 7).

Discussion

There has been no description concerning a possible mechanism for the formation of these converging zones. The most likely explanation lies in the rapid changes in the course, shape, size, and number of the converging medullary veins caused by the fast-growing crossing nerve fiber tracts, i.e., projection, commissural, and as-

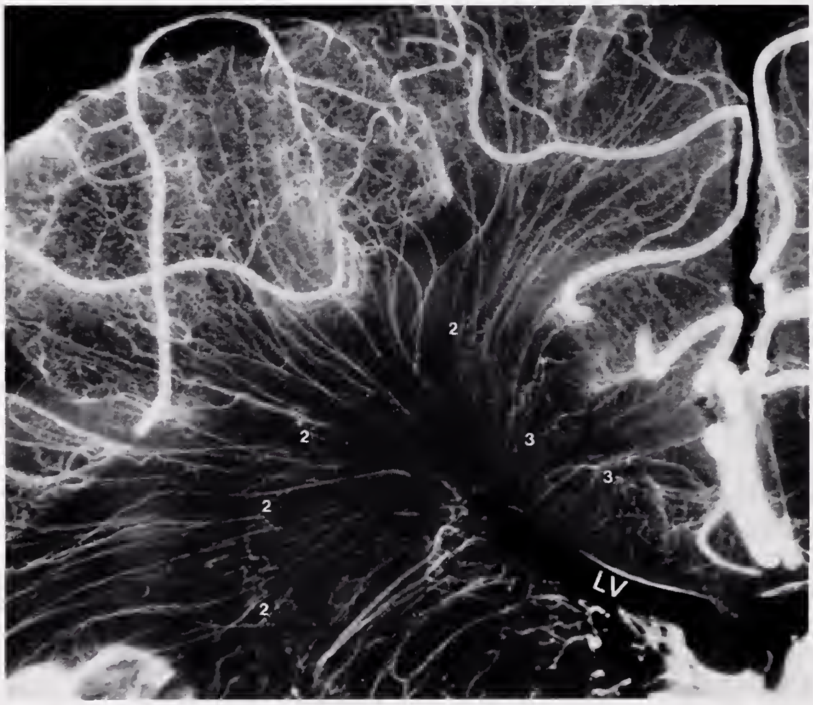


Fig. 4 Roentgenograms of a coronal injected brain slice showing pial and medullary arteries with the latter streaming toward the corner of the body of the lateral ventricle (LV). Their branching sites (2 and 3) within the centrum semiovale are similar to those of the venous candelabra and the palmate zone immediately above the corpus callosum.

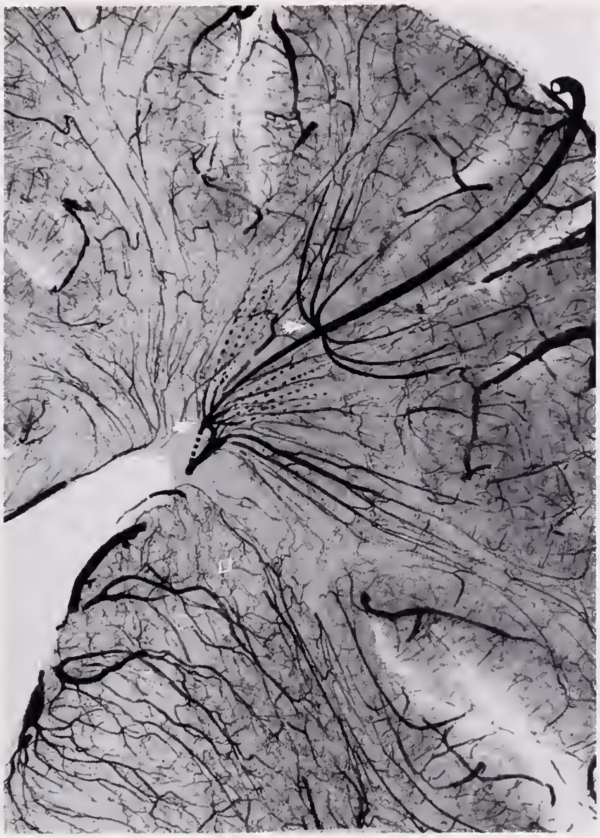


Fig. 5 Schematic drawing of a medullary venous malformation on a roentgenogram (coronal slice) of an injected specimen showing its presumptive venoarchitecture. Dotted lines indicate possible sites of occlusion, hypoplasia, or aplasia of segments of veins leading to formation of medullary venous malformation. One large and one small venous convergence pattern (white arrows) in the anteroposterior view represent a typical medullary venous malformations of superficial draining type (shape of a martini glass without stem) for which we have given a name of "double parachute sign." Partial, mild, incomplete, and intermittent occlusion of medullary, subependymal, internal cerebral, or galenic vein and/or of the straight or transverse sinus during fetal life may lead to formation of medullary venous malformation. The subependymal veins of the involved area are frequently aplastic or hypoplastic. The fine basket-shaped medullary veins are usually increased, giving an impression of hypervascularity (venous). The superficial cortical (pial) veins are frequently fewer in number and size. Also noted is stretching, thinning, and elongation of the superior striate veins by the anterior limb of the internal capusules (row of diamonds). These veins eventually open into the anterior inferior caudate tributaries of thalamostriate veins.

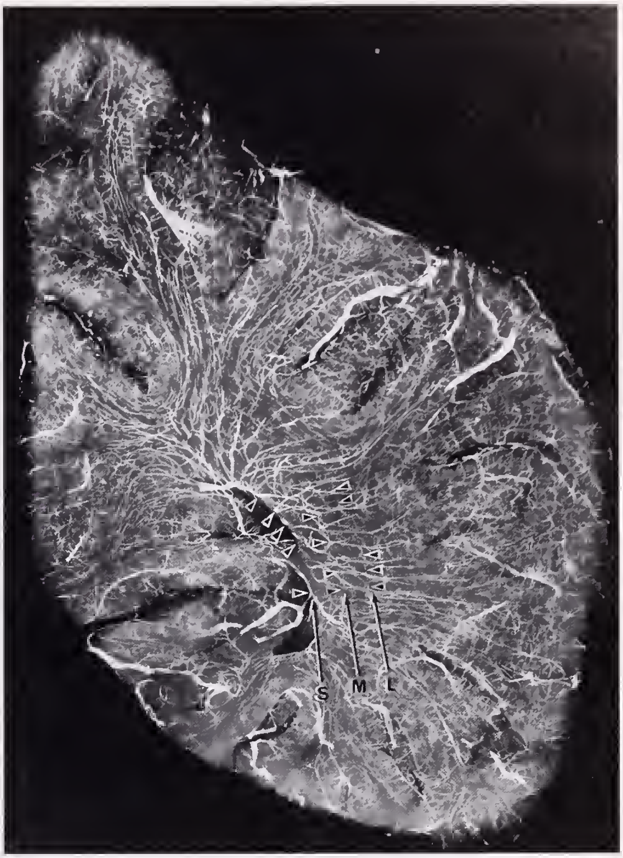


Fig. 6 Roentgenograms of a coronal slice (through the left atrial region) of an injected adult brain, showing three venous converging zones of the deep medullary veins. Unlike in the frontoparietal area, the deep medullary veins in the paraatrial area stream medially in parallel fashion toward the lateral wall of the atrium. In doing so, three zones of venous convergence (three rows of arrowhead) are created; the outer one (L) represents the lateral border of lateral sagittal stratum, whereas the middle one (M) outlines the medial border of the medial sagittal stratum (the border between the optic radiation and tapetum). The third and most medial one is the subependymal zone (S) in which the medullary veins join the lateral atrial vein (lateral atrial tributary of the inferior ventricular vein, or of the direct lateral vein).

sociation fibers which grow rapidly during intrauterine and early postnatal life. As shown in Riley's beautiful myelin-stained "atlas of the basal ganglia, brain stem and spinal cord," the nerve fiber tracts of the centrum semiovale which appeared in the coronal sections of the atlas include from outside inward: 1) the substantia medullaris cerebri; 2) the corona radiata; 3) the pes coronae radiatae; and 4) the substantia reticularis coronae radiatae (4). The fasciculus subcallosus and the fasciculus occipitofrontalis superior were also indicated in his atlas and occupy the medial and major part of the "substantia reticularis coronae radiatae." The second and third zones of convergence can be nicely fitted between the corona radiata and the pes coronae radiatae, and between the pes coronae radiatae and the substantia reticularis coronae radiatae (SRCR), respectively. The fourth (or subependymal) zone of convergence is located medial to the subcallosal fasciculus-superior occipitofrontal fasciculus complex (F Subca-FOFS. See Fig. 1). It occupies the lateral part of the subependymal glial substance. The latter is situated immediately next to the superolateral corner of the lateral ventricle. As described above, in the first zone of convergence, bamboo-branch unions and their variations appears to spread over a wide area of the peripheral white matter,

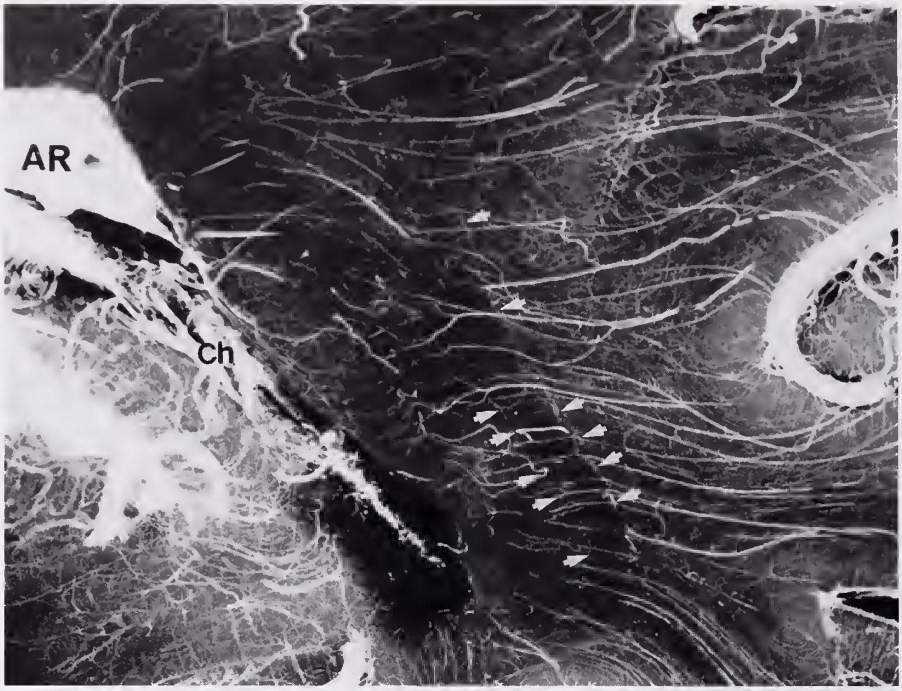


Fig. 7 Roentgenogram of an injected posterior frontal brain slice (10 mm thick) in coronal plane, showing two arterial branching zones outlining the lateral and medial borders of the optic radiation (two rows of arrows). The plane of sectioned ventricular wall between the cortical and ventricular parts of the slice is slightly oblique. (The tapetum and the subependymal veins are therefore seen as slightly oblique.) The rich blood supply of the cortical gray matter is evident. (See the vascular cortex outlined by numerous intracortical arterial branches.) Other labeled structures are the choroid plexus (Ch) of the left atrium (AR).

whereas coat-tree (or hat-rack) unions are rare and found within the frontoparietal gyral white matter (Fig. 3). Incomplete or atypical forms of these unions are observed anywhere in the hemispheric white matter, however (Fig. 2). In the para-atrial area, where the tapetum and the internal and external sagittal strata form the lateral atrial wall, two zones of venous convergence can be seen identifying the medial and lateral borders of the optic radiations (Fig. 6). The junction between the internal and external sagittal strata can not be clearly identified by injection studies. Aside from the two zones located parenchymally, there is the third (or subependymal) zone of venous convergence which is located subependymally beneath the tapetum. The last mode of union is hair brush-like. As stated, the outer two zones of venous convergence correponding to the medial and lateral borders of the optic radiation (sagittal strata) respectively (Fig. 6), can also be demonstrated in the arterial injection (Fig. 7). The arterial candelabrum (not shown) is slightly less conspicuous than the venous one in our injected specimens (Fig. 4). When the medullary arteries and veins (5) are pierced by major fiber tracts, the vessels become stretched, straightened, thinned out in caliber, and more separated. This is caused by progressive compression and separation of these arteries and veins by the rapidly growing penetrating fibers during fetal and early postnatal life. These changes are well seen in the region of the corona radiata, the corpus callosum, the internal capsule, and the optic radiations. The changes are particularly conspicuous in the course of the anterior inferior caudate tributaries of the thalamostriate veins (Fig. 5) or of the lenticulostriate arteries running through the anterior limb of the internal capsule (5).

As described in 1987 by Boley et al. (6) and as shown in Fig. 10, in “vascular ectasia of colon in the elderly,” the veins passing from the mucosa to serosa through the muscular layer of the colon, especially the caecum, can be compressed by an increased abdominal pressure or intraluminal pressure of the caecum during straining, coughing, or constipation. Sudden changes in venous pressure, transmitted in retrograde fashion, from the vein to the neighboring venules, then to capillaries, to arterioles and even to arteries, become associated with the enlarged capillary networks, particularly when the venous obstruction is partial, mild, repetitive, and long lasting. This may eventually lead to formation of arteriovenous shunts, mimicking aquired malformation in the elderly. Indeed, in angiograms of such cases in our series, the enlarged arterial feeders from the

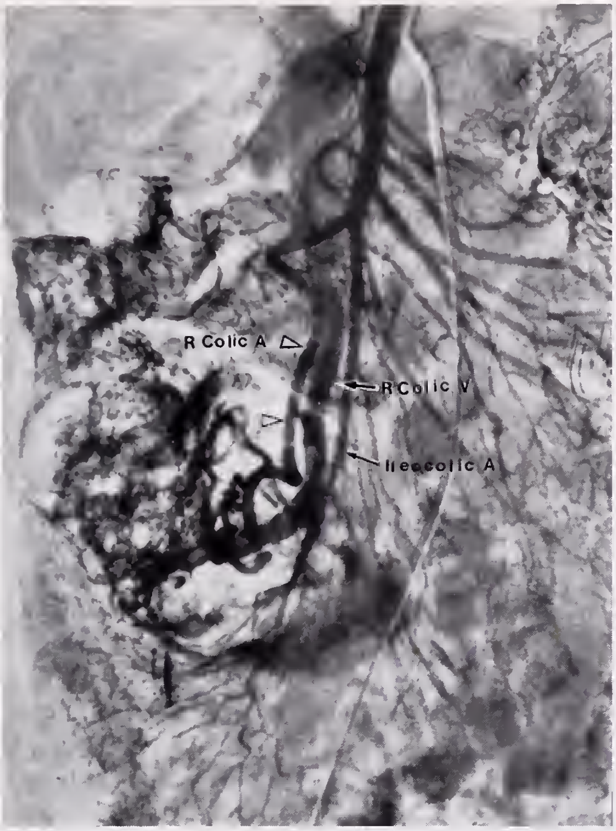


Fig. 8 A case of low intestinal bleeding in an elderly patient secondary to vascular ectasia of the caecum is presented. A superior mesenteric arteriogram shows contrast filling of both right colic (R colic A) and ileocolic arteries (ileocolic A) and right colic vein (R colic V) in the arterial phase and vascular brush involving the caecum mimicking an arteriovenous malformation.

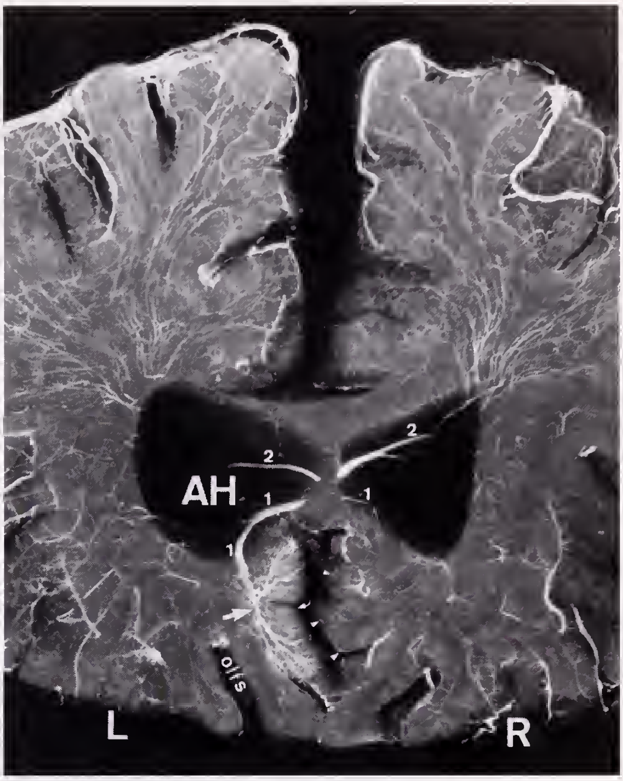


Fig. 9 Medial inferior frontal medullary venous malformation discovered in a roentgenogram of a coronal brain slice of an injected specimen. (Injection was made only into the venous system.) Incidentally found was a medullary venous malformation of deep draining type (large arrow). On the normal side (R), a few pial veins outline the cortex of the subcallosal part of the cingulate and rostral gyri (unlabeled white arrowheads). The total thickness of the cortex beneath can be clearly estimated by the injected fine intracortical veins. On the other hand, on the left side, total opacification of the corresponding gyri to the very cortical surface occurs. (A small curved arrow indicates the contrast filling presumably to the very first cell layer of the cortex.) Note that no pial (cortical) veins were visualized on the pathological area where the cortical veins were presumably once occluded (or never developed?). The excess vascularity of this medullary venous malformation appears to far exceed that of the normal neighboring area with a disproportionately larger (than normal) central medullary draining vein (large arrow) which opens into the inferior septal vein (1). It is likely at one time cortical veins of the pathological area became occluded (at least partially, initially with subsegment alternating stenosis and reopening of the cortical veins). Once the deep medullary veins take over the area normally drained by the superficial medullary, subcortical, and intracortical veins, the necessity of the cortical veins ceases to exist. A medullary (capillo)venous malformation is thus created once a pressure equilibrium is established. Therefore, the venous pressure within the lesion should be normal (or in rare cases barely higher than normal) after so many years postnatally. The superior septal vein (2), olfactory sulcus (olfs), right (R), and left (L) sides of the specimen are also labeled.

right colic artery, the dilated veins draining into the right colic and ileocolic veins, and the dilated in-between vascular networks (which are indeed indistinguishable from malformations) were observed (Fig. 8).

We believe that a similar mechanism can be applied in pathogenesis of medullary venous and at least in some (if not many) cases of other cerebral vascular malformations. When there is a partial, incomplete, repetitive collapse and reopening of pial, medullary, or subependymal vein(s) or dural sinus(es), occurring during early fetal life, any increase in venous pressure of the involved veins may extend similarly in retrograde fashion to the neighboring venules, capillaries, arterioles, and arteries. When this chain reaction repeats itself many times, the capillary networks and the adjacent more proximal vascular segments may become dilated and eventually lead to formation of 1) medullary venous malformation with involvement of medullary veins only, 2) medullary venous malformation with capillovenous component, 3) medullary venous malformation with medullary arterial component, 4) medullary venous malformation with arterial component or even frank malformation of localized or even diffuse form. This depends on the degree and extent of the retrograde involvement. The key factors seem to lie in 1) partial obstruction, 2) fluctuating venous pressure, and 3) long duration. The cause

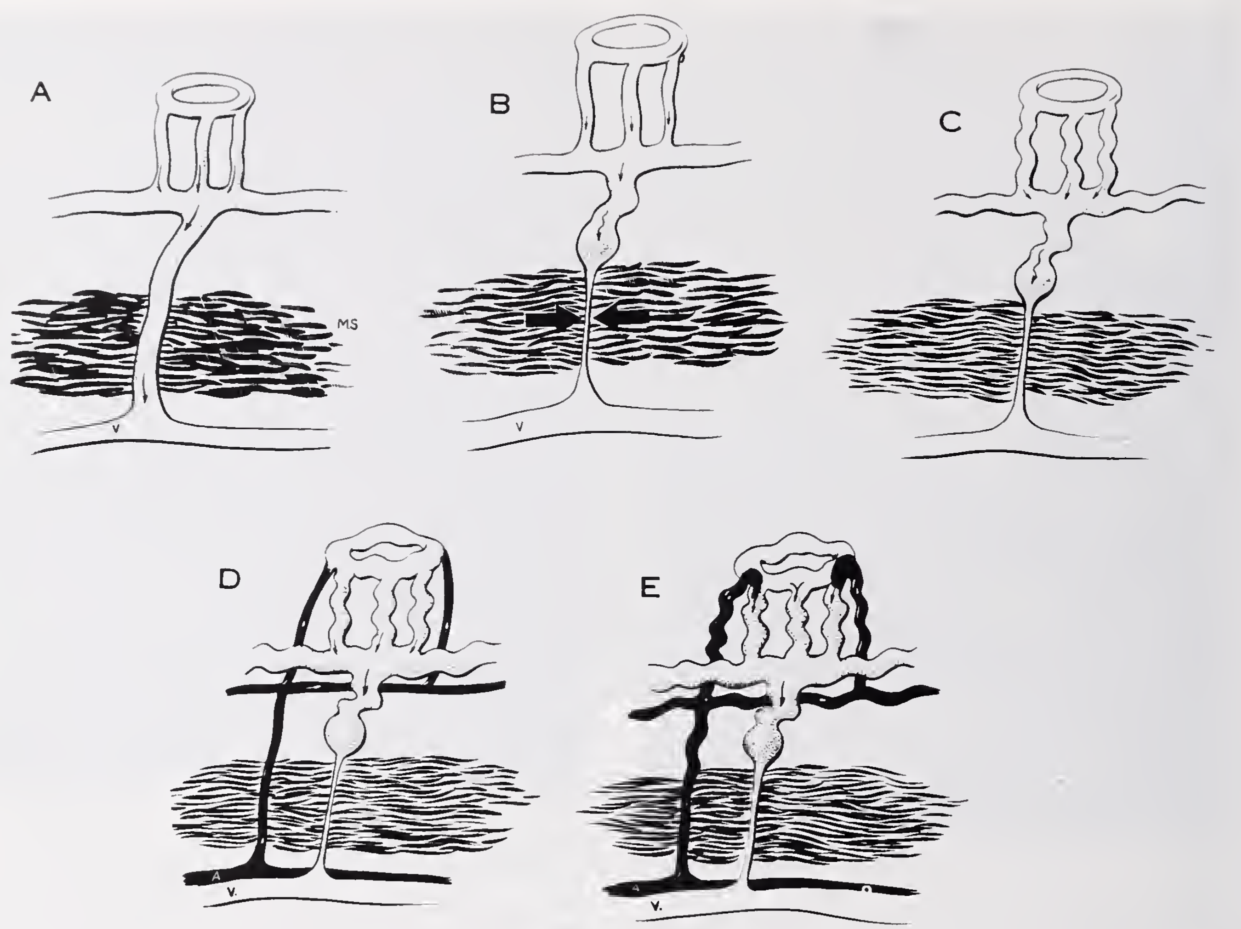


Fig. 10 This diagrammatic representation shows a likely mechanism of development of caecal vascular estasia in an elderly patient. (A) normal state of colonic vein passing from the mucosa to serosa through muscular layer; (B) muscular contraction or increased intraluminar pressure causing venous obstruction; (C, D) the submucosa; veins, venules, and capillaries become dilated in retrograde fashion; (E) eventually the capillary ring becomes dilated, the precapillary sphincter becomes incompetent and small arteriovenous communication is developed through the ectasia (6). (With permission. Courtesy of Gastroenterology 1977).

of venoocclusive disease could be dehydration, coagulation abnormalities, (venous) angiitis, etc. with an additional aggravating factor of changing maternal abdominal pressure affecting fetal intracranial venous pressure, etc.

As mentioned previously (3), in most (if not all) cases of medullary venous malformations, the number of dilated medullary veins within the malformation far exceeds the normal expected number of medullary veins (Fig. 9). Indeed, it has a far more venous (and capillary) vasculature than needed for a mere compensation for the occluded (or hypoplastic) area. Indeed, the central medullary vein of a medullary venous malformation and its pial extension is usually moderately to markedly enlarged, and in some cases it may be greatly dilated or ballooned, with narrowing of the distal pial vein immediately before opening into the dural sinus (3) (Fig. 11). This narrowing could also be the very site of the original pathology with intermittent occlusions leading eventually to formation of a medullary venous malformation. Moreover, rare but occasional bleeding from the malformations (in addition to frequent association of other venous occlusion) suggests that the venous pressure of the involved area may remain slightly higher than in other normal areas, although after so many years postnatally the venous pressure of the medullary venous malformation is more likely to be in a state of or at least near a state of equilibrium with the central medullary vein which has remained dilated since its onset in the fetus. Many recent reports have emphasized a frequent association of medullary venous malformations with cavernous malformations (cavernous angioma). Although gene factors undoubtedly play a role in formation of cavernous malformations in some cases (particularly in familial cavernous angiomatosis) (7, 8), these hemorrhages could be a mere expression (or residue) of a tiny bleeding or bleedings in the medullary venous malformations. We have experienced such

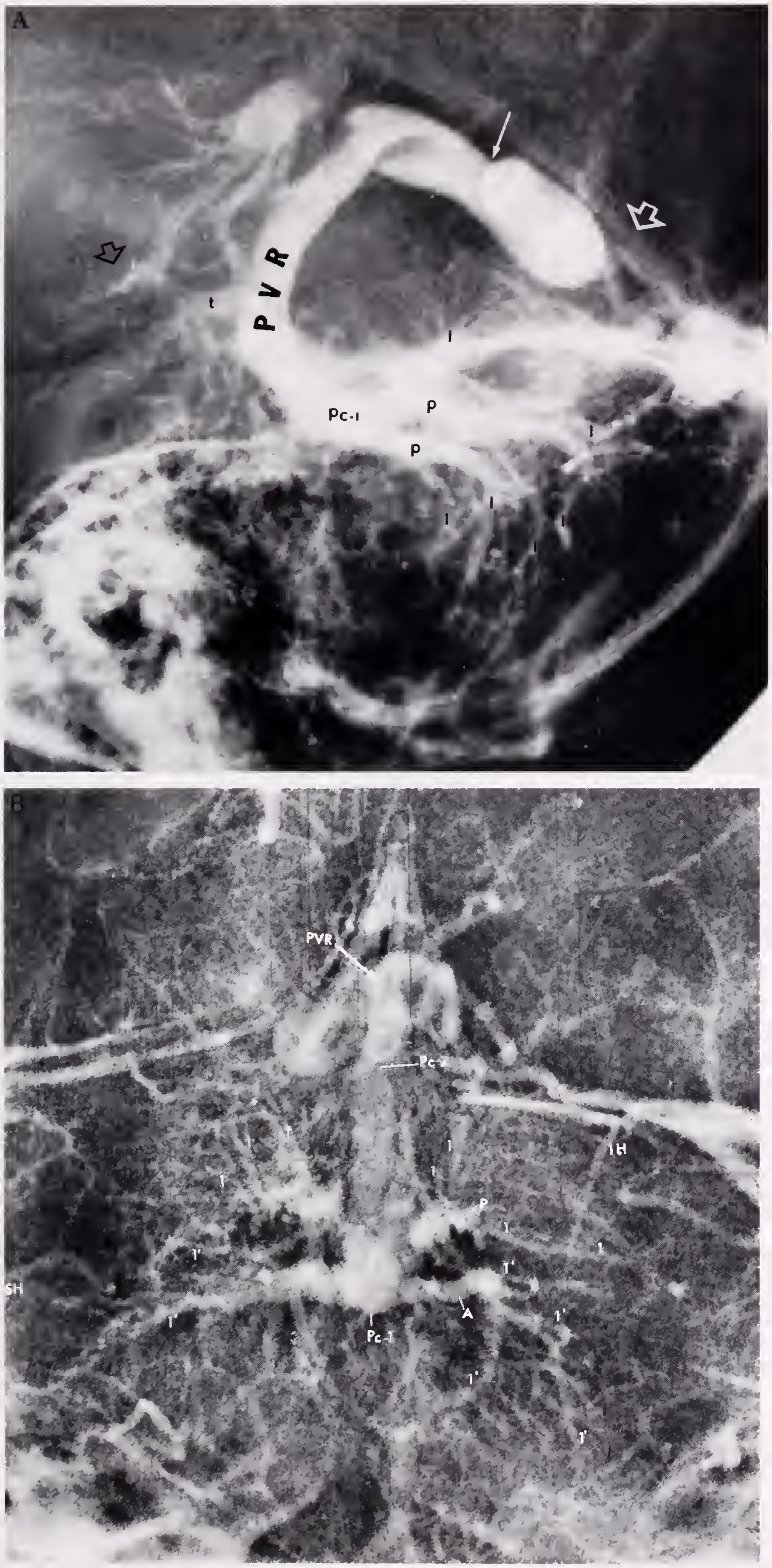


Fig. 11 Cerebellar medullary venous malformation with markedly dilated central draining vein. A very large precentrovermorectal vein (PVR) drains a huge vascular malformation involving cerebellar hemispheres, vermis and dorsal mesencephalon (black empty arrow). (A) Vertebral angiogram, venous phase, lateral view; (B) same case, Towne view. The ballooned PVR drains most of the vermis and cerebellar hemispheres on both sides (1) and converges into four main stems before opening into the first segments (Pc-1) of the PVR. Initially, the venous blood flowed through a precentral cerebellar vein (Pc-1). This vein, instead of opening into the vein of Galen, now continues to course backward and downward over the declive of the vermis before it joins either the straight sinus or the torcular via declival vein (open white arrow). Note a narrowing of the most distal segment of the ballooned draining vein (end of the ballooned PVR, open arrow). The unlabeled arrow indicates the tortuous dilated and looped pial vein before it enters the straight sinus or torcular via declival vein. Note the slightly prominent tectal vein which joins the vein of Galen (open black arrow). Practically all vermian veins course centrally instead of outwardly to join the hugely ballooned precentrovermorectal vein. Also note the markedly increased (venous) vascularity within the lesion.

cases with repeated tiny new hemorrhages in different parts of medullary venous malformation mimicking cavernous angiomatosis (Fig. 11). As described by McCormick (9), medullary venous malformation can be of microscopic size. Bleeding into these lesions may give an appearance of telangiectasia or cavernous malformation with hemosiderin in magnetic resonance images. The term "venous angioma" is not suitable because it has a connotation of neoplasm. The term "medullary venous malformation" was recommended (3), because all medullary venous malformations have a component of numerous converging fine but dilated medullary veins and a greatly dilated central medullary vein or veins presumably originating in early fetal age. In "developmental venous anomalies" of Lasjaunias et al. (10), the venous blood is supposed to flow simply from a high- to a low-pressure area with no apparent pathological changes. In addition, there is no or almost no gliosis or scar tissue formation on pathological examination. For these reasons, the proponents of the latter term (developmental venous anormalies) have concluded that medullary venous malformations are a simple venous anomaly and do not derive from an occlusive condition. As described above, increased capillovenous vascularity (Fig. 9) within the medullary venous malformation (occasionally with arteriolar or frank arterial component) (3), not infrequent association of other venous abnormalities, such as stenotic or prestenotic ballooned segment, and/or narrowing (or occlusion) of the adjacent or distal dural sinus, all point to the possibly occlusive nature of the disease processes. When there is an arteriolar or arterial component, the circulation within the lesion is generally more rapid.

According to Ikuta (11), repair processes of a pathological lesion in the adult is left with astrocytosis and with formation of a "scar tissue." In young fetal brains, cells are not bound together and are able to move freely. The extracellular spaces are much wider in young fetuses who are in no need for creating edema to have a wider extracellular space for removal of degenerated dead neurons. For this reason, outward migration of neuroblasts along the radial fibers to form the various cell layers of the cortex occurs with ease. Lesion repair in young fetuses therefore results in formation of anomalous brain tissue whereas in mature brains it results in astrocytosis and scar tissue. The fact that no intracerebral scar tissue or gliosis was detected may not become a refutation of venoocclusion as a cause of medullary venous malformation in young fetuses.

Although the above-stated postulate is still far from proven, we believe that this explanation of pathogenesis is applicable to most cases of medullary venous malformations and some cases of other cerebral vascular malformation. Gene factors (chromosome 7) and faulty angiogenesis may play a role in formation of cerebral vascular malformation.

References

1. Huang YP, Wolf B. Veins of the white matter of the cerebral hemisphere (the medullary veins). Am J Roentgenol Radium Ther Nucl Med 1964; 92:739–755.
2. Huang YP, Okudera T, Maehara F. White matter angioarchitecture with a view to the pathogenesis of medullary venous malformations. In: Bigot JM, et al, editors. Radiology: Proceedings of the 17th International Congress of Radiology; 1989 July 1–8; Paris, France. New York: Elsevier Science Pub. Co.; 1990: 563–570.
3. Huang YP, Robbins A, Patel SC. Cerebral venous malformations and a new classification of cerebral vascular malformations. In: Kapp JP, Schmidek HH, eds. The cerebral venous system and its disorders. Orlando, FL: Grune&Stratton; 1984: 373–474.
4. Riley HA. An atlas of basal ganglia, brainstem and spinal cord based on myelin-stained material, 2nd. ed. New York: Hafner Publishing Co.; 1960.
5. Kaplan HA, Ford DH. The brain vascular system. Amsterdam: Elsevier Science Publishers; 1966.
6. Boley SJ, Samartano BS, Adams PA, Di Biase A. On the nature of etiology of vascular ectasia of the colon: Degenerative lesion of aging. Gastroenterology 1987; 72: 650–660.
7. Rigamonti D, Drayer BP, Johnson PC, et al. The MRI appearance of cavernous malformations (angiomas). J Neurosurg 1987; 67:518–524.
8. Günel M, Awad IA, Fiberg K, et al. A founder mutation as a cause of cerebral cavernous malformation in hispanic americans. N Engl J Med 1996; 334:946–951.
9. McCromick WR. Cryptic vascular malformation of the central vernous system. J Neurosurg 1966; 24:865–875.
10. Lasjaunias P, Burrows P, Planet C. Developmental venous anomalies (DVA): The so-called venous angioma. Neurosurg Rev 1986; 9:233–244.
11. Ikuta F. The process of brain lesion repair and activity of astrocytes. In: Ikuta F, ed. Neuropathology in brain research. Amsterdam: Elsevier Science Publishers; 1991: 211–231.

Operative Microphotography:

A Malis Legacy

Richard J. Radna, M.D., Ph.D., and Ved P. Sachdev, M.D.

Abstract

An account of the methods and equipment used by Dr. Malis for the development of operative microphotography is presented. Attention to the critical evaluation of technology became part of the legacy provided to those he trained. Current microphotographic innovations are described. **Key Words:** photography, microsurgery, operating microscope.

Editor's note: Dr. Radna distinguished himself by receiving a Masters degree from Hunter College, an M.D. degree from the Mount Sinai School of Medicine, and a Ph.D. degree from the City University of New York, all in 1973. After completing his neurosurgical training at The Mount Sinai Hospital, he was awarded the Charles A. Elsberg Fellowship by the New York Society Academy of Medicine in 1981 and again in 1983.

Dr. Sachdev began his studies at Punjab University in India. He became a Fellow of the Royal College of Surgeons after completing his training in otolaryngology at the College of Physicians of London. A residency in Neurosurgery at The Mount Sinai Hospital followed between 1970 and 1973. His current academic title is Clinical Professor of Neurosurgery.

Leonard I. Malis brings to neurosurgery a profound knowledge of mechanical, electrical, and optical engineering, in addition to an extraordinary background in neurophysiology and neuroanatomy. Of no surprise to his colleagues, he is a master photographer both in and out of the operating room. After summarizing the methods and equipment used by Dr. Malis for illumination and photography through the operating microscope (1, 2), the authors describe further advances.

Microscopic Equipment

Dr. Malis initially brought the microscope into the operating room at The Mount Sinai Hospital in 1965 to facilitate the removal of lesions at the base of the skull (3, 4). The microscope for the first case was borrowed from ear-nose-and-throat colleagues and was quickly replaced by a Zeiss Opmi 1 which Dr. Malis purchased (5–9).

The Opmi 1 was progressively enhanced for neurosurgical operations. Two extension arms were added to give an excursion of 53 inches from the base to the scope head. Because the incandescent bulb generated too much heat within a gas-sterilized drape bag, Dr. Malis developed a cooling system using standard wall suction and flexible anesthesia tubing as a vent. To prevent bulb burnout during a surgical procedure and lengthy redraping, the bulb was changed on the first day of each month. The base of the Zeiss stand was stabilized by lead bricks bolted in place. Dr. Malis also designed and built a motor for the focus drive.

A 300-mm objective, a 125-mm binocular, and 20× eyepieces were in standard use with the Opmi 1. The purpose of this configuration was to give the shortest length from the surgeon to the operative field, while allowing adequate magnification and working distance. The incandescent light source provided an illuminated field of 4 cm.

From the Department of Neurosurgery, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029. Address reprint requests to Richard J. Radna, M.D., Ph.D., 1165 Park Avenue, New York, NY 10128.

Magnification ranged from 3× to 20× with analogous fields ranging from 9 mm to 6 cm. Straight binoculars were used for transphenoidal, prone-oblique, and semisitting positions; Dr. Malis favored the semisitting position for posterior fossa and posterior cervical approaches. Angled binoculars were used with the patient in the supine and prone positions. He basically thought that nothing should change from case to case except the binoculars.

Dr. Malis continued to use Zeiss microscopes. To enhance the light provided, he added to his Opmi 1 configuration a halogen auxiliary fiberoptic light source delivered via the Vertolux prism mounted externally on the objective lens (2). The prism has the advantage of illuminating the underside of a complex surgical field more fully than the coaxial system alone. The yoke-mounted incandescent light was subsequently replaced by a fiberoptic coaxial light delivery system, and then by the Zeiss fiberoptic retrofit for input to the coaxial lighting system. The need for a light source within the drapes was thereby eliminated.

Dr. Malis began using a Zeiss Opmi 1 microscope with a 50-50 beam splitter which permitted a Zeiss photo adapter on the left side and an assistant's monocular viewing tube on the right. When he added his first black-and-white television camera in 1967, he eliminated the assistant's viewing tube to allow space for the television camera and added television monitors on the operating room walls. Dr. Malis then designed and built a television distribution system which carried the television picture to the monitoring room, the residents' room, the neuroradiologists' reading room and office, and his own departmental office, with the availability of two-way sound. This arrangement was continued and upgraded when color television replaced the black-and-white in 1970.

When the Zeiss binocular assistant viewing tube became available, it became possible for the assistant to actually assist instead of just observe. Dr. Malis then placed the new binocular assistant unit on the right side, and the 35-mm still camera and the television camera on the left side. The still camera and the television camera were coupled through a unit he built using a mirror flipped by hand through the plastic drape to shift between the television and the still camera. He designed the lens system which matted the photographed field to the television field and the surgeon's microscope view.

Dr. Malis based his standard on a 1-second time exposure, with the anesthesiologist holding the respiration to prevent slow movement blur. Cardiac systole gives a vascular movement lasting less than 0.1 second, too brief to blur the photograph in an exposure lasting 1 second. The Zeiss-Urban prism beam divider was then developed to couple the still and television cameras, and the mechanically flipped mirror unit could be discarded. The exposure time was increased to 2 seconds to make up for the prism dividing the light.

The original 35-mm camera back had only manual film advance, which was accomplished with a sterile clamp. When automatic film advance became available, the camera backs were replaced with modern 35-mm cameras. Exposure was controlled, however, by using the iris diaphragm on the camera coupler on the microscope. This could be done readily by hand, using the television picture as the reference. Because of the small iris opening that the long exposure permitted, depth of field was enhanced. The basic principle was that the taking of the photographs required neither significant time, effort, or knowledge by the operating surgeon. The camera set-up had been designed so that all that was required was to tell the anesthesiologist to hold the respiration and, when the anesthesiologist said "holding," the cable release was pushed.

Dr. Malis took all his photographs as stereo pairs by simply moving the microscope about 2.5 inches laterally, recentering it on the same point in the field, and taking another picture. Almost all the residents and staff were skilled in cross-eye stereo, because in the era before computed tomography and magnetic resonance imaging, all of our radiologic procedures were done in stereo pairs and were placed on the view boxes so that the entire group could simultaneously see the material stereoscopically. Accordingly, in the neurosurgical conferences, the operative photographs were projected by a pair of carousel projectors onto adjacent screens and were viewed in stereo by the cross-eye technique.

When the Zeiss Universal Stand became available, Dr. Malis made a change but maintained the Opmi 1 microscope with his power focus, using the internal tungsten halogen light sources of the new stand which had increased stability, maneuverability, and simplicity. Although Dr. Malis had designed the magnetic latches for the Yasargil Contraves Microscope stand, he continued to use the Zeiss Universal Stand for his own surgery because of a difference in operative techniques. Dr. Yasargil often stood and moved rapidly around the operative field from many angles for which the Contraves was ideal. Dr. Malis, on the other hand, regularly sat, rarely moved, and preferred the stability of the Universal Stand.

Further Progress in Operative Microphotography

The dogma that Dr. Malis taught his students was that the last reason you should do anything in neurosurgery is "that is the way everybody else is doing it." Therefore, with progression of the technology in the operating microscope, the following text summarizes the techniques currently being used by the authors for operative microphotography. These techniques are to a great extent enhancements which follow the principles proposed by Dr. Malis (1), and made possible by further development in surgical light sources and delivery systems.

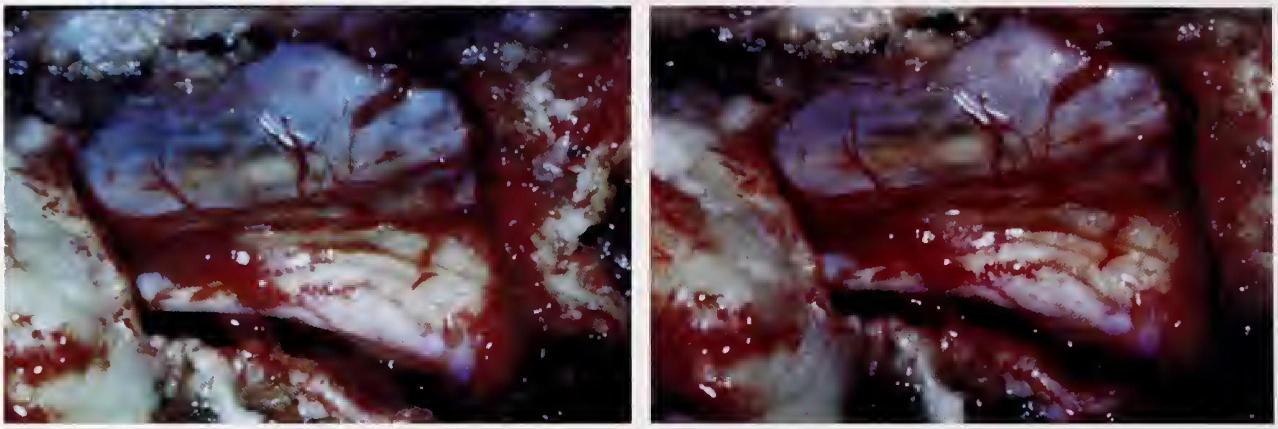
The Zeiss Superlux 40 gives two times the light output of the Dyonics source, with a color temperature of 4400 K (Minolta Illuminance Meter T1H, Minolta Color Meter IIIF, Minolta, Inc., Ramsey, NJ). The Zeiss xenon Superlux 300 provides four times the light output of the Dyonics source, and delivers this light at a color temperature of 5000 K, approximating the daylight color temperature of 5600 K. With the use of the flash mode, the output of the Superlux 300 gives a color temperature approaching 5600 K. In addition, in microscopes such as the Zeiss NC2, the Variolux and Variospot light-collecting systems tailor the size of the illuminated field to that of the visual field of the surgeon, concentrating the light where needed. (Particularly for photographic applications, for the uniformity of illumination is important to keep the illuminated field 1/3 greater in dimension than the surgical field, because the light delivery systems concentrate most light toward the center of the illuminated field.) These enhancements allow an approximately 10-fold increase in the light delivered to the surgical field relative to the aforementioned Opmi 1 configuration, giving an illuminated field of 30,000 foot-candles, using an objective focal distance of 350 mm and a 7-cm illuminated field. With this amount of light, the heat generated requires frequent irrigation of neural structures to prevent drying.

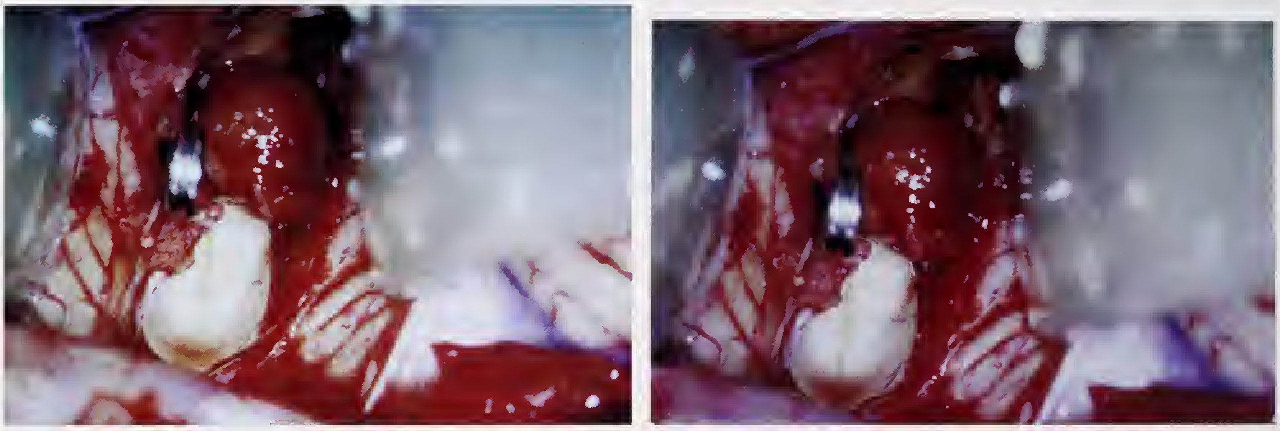
The increase in the amount of light delivered by progress in light sources for the surgical field has the major advantage of allowing use of the binocular iris diaphragm, which considerably increases depth of field, diminishes the need to focus the microscope, saves operating time, and eliminates glare. Because of the intrinsic diminution in depth of field with higher magnifications, the iris diaphragm is needed to make a depth of 6 cm crisply in focus. The full diaphragm opening is 15 mm, which would be equivalent to a microscope not including the iris diaphragm. The authors ordinarily use an iris opening of 6 mm for surgery, with photographs being shot with an iris as small as 1 mm. Photographs shot with the iris diaphragm closed down lead to crisp, clear images over large excursions of depth, and therefore enhance the value of depth perception in stereo operative photographs (Fig. 1). In contrast, the stereo operative photographs with less depth of field shown in Fig. 2 use a more fully open iris with a less luminous light source and a shorter exposure than used in Fig. 1.

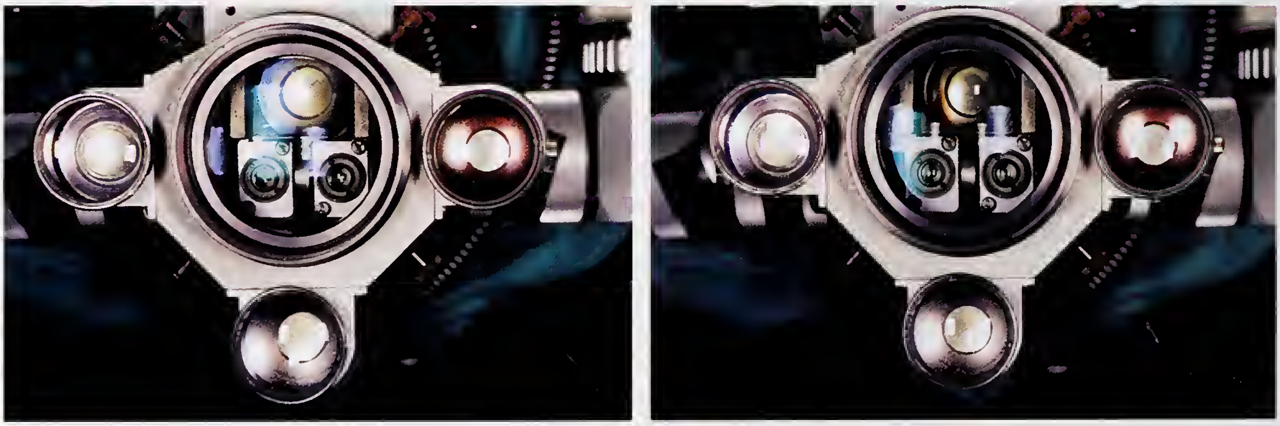
In systems with the Opmi 1 microscope, we have enhanced light by upgrading to the Opmi 11 which has a collector for light intensification in coaxial light delivery. Three auxiliary Zeiss bell illuminators (Gefa Instrument Corporation, Garden City Park, NY) (Fig. 3) mounted on the objective are used, each illuminated with one Dyonics light source. The bell illuminators, mounted around the circumference of the objective lens, provide greatly enhanced light uniformity in a complex surgical field, in a manner analogous to that of the Vertolux externally mounted prism of the Opmi 1. The illuminated field size of the bell illuminators can also be adjusted to enhance light delivery at higher magnifications and smaller fields. Four Dyonics illuminators achieve 30,000 foot-candles of light delivered at a distance of 350 mm from the objective, with an illuminated field of 7 cm. The light output of 4 Dyonics light sources is equivalent to that of one Superlux 300. The use of four light sources contributing to the illuminated field essentially solves the problem of intraoperative bulb burnout. The Superlux 300 also has safety features in this regard, because bulb burnout is designed to occur on powering up the light source. The aforementioned auxiliary bell illuminators can also be used with one Superlux 300 and a quad-furcated fiberoptic cable.

Where the Dyonics light source is used with a tungsten temperature, no photographic filter is required with tungsten 160 ASA film (Figs. 1 and 2). Because of the color temperature of the Superlux 40 and Superlux 300, an 82C filter is used with daylight film. Without the 82C filter in the camera-microscope adapter, white structures appear yellow. In Superlux 300 flash mode, a filter is not necessary while using daylight film. The 82C filter does attenuate light delivery to the camera by 1/3 stop and slightly attenuates photographic clarity (10).

The authors have maintained a 1- to 2-second exposure for dry surgical fields, which gives optimal clarity and depth of field. The 2-second exposure causes a slight color distortion, but allows the use of a smaller iris, which greatly enhances depth of field (Fig. 1) (11). If there is a field with







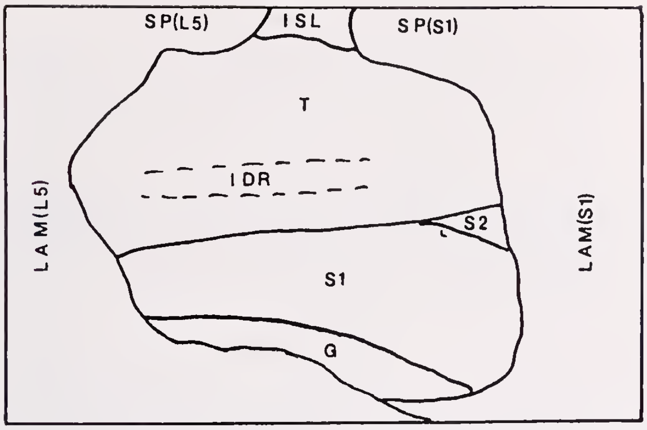


Fig. 1. Stereo view of a decompressive laminotomy/facetectomy at the L5/S1 level on the left side. These photos were shot simultaneously with two stereo cameras (Fig. 4), mounted on a Opmi 11 microscope body, with coaxial light and auxiliary bell illuminators using four Dyonics light sources (Figs. 3 and 4), with 30,000 foot-candle illumination intensity. A 2-second exposure was used, with an iris opening of 2 mm, leading to an extended depth of focused field. LAM(L5), Lamina L5; Lam(S1), Lamina S1; S1, S1 root; S2, origin of S2 root; IDR, intradural root; SP(L5), spinous process L5; SP(S1), spinous process S1; ISL, interspinous ligament; G, epidural gelfoam; T, theca.

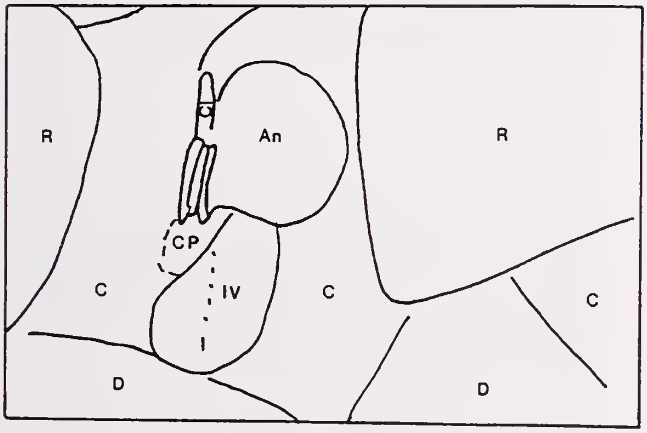


Fig. 2. Stereo view of a vermian approach for clipping of a distal pica aneurysm. These photos were shot with a single camera, which was repositioned manually for the second shot of the stereo pair. Although the stereo view achieved is adequate, the horizontal alignment for ease of stereo viewing is not as exact as seen in Fig. 1, where two stereo cameras were used. The depth of focused field is less (note the blurring of the retractor blade and proximal cerebellum) than that seen in Fig. 1, as an iris of 6 mm was used with an exposure time of 1 second and a light intensity of 4000 foot-candles. (The Opmi 1 microscope with the two coaxial light path and Vertolux prism was illuminated by two internal halogen light sources of the S3 universal stand.) An, aneurysm; Cl, clip across aneurysm's neck; CP, choroid plexus; IV, floor of fourth ventricle; C, cerebellum; D, dura; R, retractor blades.

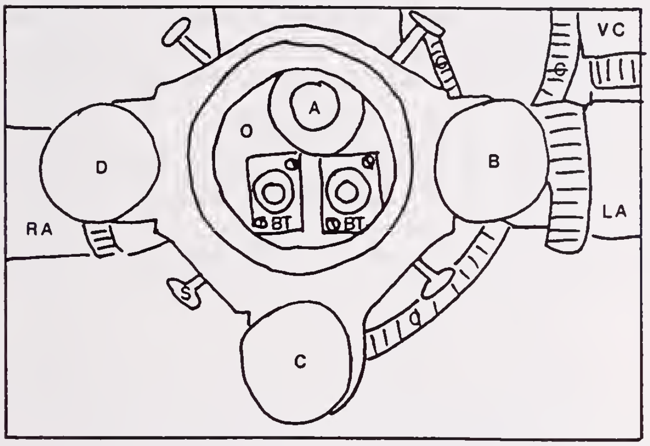


Fig. 3. Stereophotographic view of an Opmi 11 objective lens, surrounded with three bell illuminators at 90, 180, and 270 degrees, taking the coaxial light trajectory at 0 degrees. This system illuminates well a complex surgical field, such as the undersurface of the spinous process in Fig. 1. A, coaxial illuminator; B, C, D, auxiliary bell illuminators at 90, 180, and 270 degrees; BT, binocular Galilean telescopes; RA, right video/35-mm camera adapter; LA, left video/35-mm camera adapter; VC, video camera; C, fiberoptic cables for bell illuminators; O, objective lens; S, thumb screws to secure the bell illuminator assembly around the objective lens.

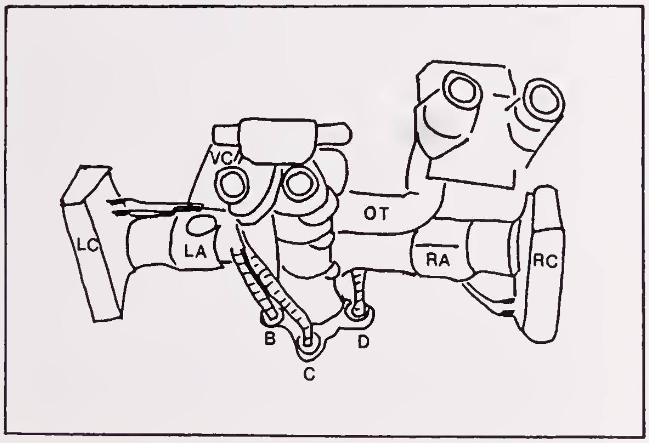


Fig. 4. Stereo photographic view of an Opmi 11 microscope equipped with stereo 35-mm cameras and dual "C" mounts for stereo video cameras. In this configuration, the documentation instrumentation receives 50% of the light, with 40% to the surgeon, and 10% to the assistant. Dual 85-mm/340-mm focal length (video/35-mm camera) adapters are used, with serial 50%/50% and 20%/80% beam-splitters. RC, right 35-mm camera; LC, left 35-mm camera; OT, observer tube; other captions as in Fig. 3.

a slight venous ooze, and a shorter exposure is considered optimal to reduce accumulation of blood in the photographic field, a 1/4-second exposure is used. For fields in which there is brisk bleeding, and an operative photograph is desired, a 1/10-second exposure is used to capture the field relatively bloodlessly. At the 1/10-second exposure, respiration does not have to be held. To facilitate adjustment of the iris diaphragm to the appropriate amount of light with the three different exposure times, the authors have externalized the analog output of a Canon T70 camera body light meter. We use the camera in the automatic mode and indirectly choose exposure time by changing the manual iris diaphragm. Because operative work is carried out at an iris setting (6 mm) appropriate for the 1/4-second exposure, photographs at this speed can be performed simply by holding respiration and shooting without iris adjustment. When desired, the advantage of longer exposures with a smaller iris is to enhance depth of field. We also use an external event-meter to give the surgeon the number of exposures taken on the roll of film and dual stereo-mounted cameras (Fig. 4), so that stereo photographs can be taken without the time required for repositioning the microscope. Two cameras also increase the number of shots possible for one case from 18 to 36 stereo pairs. The assistant's side binocular is maintained through a 20/80 beam splitter mounted on top of the 50/50 beam splitter. The extra beam splitter has not been problematic in terms of the surgeon's reach, except in the semi-sitting position, for which only one beam splitter should be used. The semisitting position also should use the straight 125-mm eyepiece holder to diminish the distance from surgeon to the field, as the 0–180 Zeiss ocular holder increases the length of the scope and leads to tiring of the surgeon's arms when in the semisitting position. The length of the scope can also be diminished by using relatively shorter, higher magnification oculars. The available 20× ocular (for the straight 125-mm binocular) and 16× ocular (for the 175-mm variangle binoculars) also have the advantage of making both 35-mm photographic and video views more inclusive of the surgical field by slightly attenuating the size of the surgical field relative to the 35-mm camera/video fields.

With advances in stereo-video recording and display, video in the hands of some microsurgeons is now replacing 35-mm photography. Advantages for the use of the 35-mm camera through the microscope remain, however. For projection and publication, a microphotograph has higher resolution than a high-resolution video (Figs. 1 and 2). A stereo pair of photographs can be taken in seconds, not disrupting the surgical procedure to any great extent. Currently available video hard-copy procedure takes considerably more time, and therefore is not as convenient for intraoperative use. At this juncture, the techniques of stereo-video and stereo-35-mm photographic documentation complement one another.

Conclusion

The level of technology which Dr. Leonard I. Malis brought to his operating room, from the day he first became a neurosurgical resident in 1947 to that of his last craniotomy in 1995, has always been on the cutting edge. The legacy that he has given his colleagues is to continue to critically evaluate and utilize technology to advance neurosurgical knowledge and to enhance the results provided to our patients. That legacy includes surgical microphotographic documentation of his neurosurgical procedures, which continues to enable neurosurgical colleagues to be enlightened and guided by Dr. Malis' operative methods, approaches, and achievements.

Acknowledgment

The insightful assistance of Mr. Peter Hoerenz of Carl Zeiss, Inc. in suggesting the use of bell illuminators and many other enhancements for the microscope is greatly appreciated.

References

1. Malis LI. Neurosurgical photography through the microscope. Clin Neurosurg 1981; 28:233–245.
2. Malis LI. Instrumentation and techniques in microsurgery. Clin Neurosurg 1979; 26:626–636.
3. Decker RE, Malis LI. Surgical approaches to midline lesions at the base of the skull: A review. J Mt Sinai Hosp 1970; 37:84–102.
4. Malis LI. New trends in microsurgery and applied technology. In: Pluchino F, Broggi G, eds. Advanced Technology in Neurosurgery. New York: Springer-Verlag; 1988.
5. Lang WH, Muchel F. ZEISS Microscopes for Microsurgery. New York: Springer-Verlag; 1981.
6. Hoerenz P. The operating microscope. I. Optical principles, illumination systems, and support systems. J Microsurg 1980; 1:364–369.
7. Hoerenz P. The operating microscope. II. Individual parts, handling, assembling, focusing, and balancing. J Microsurg 1980; 1:419–427.
8. Hoerenz P. The operating microscope. III. Accessories. J Microsurg 1980; 2:22–26.
9. Hoerenz P. The operating microscope. IV. Documentation. J Microsurg 1980; 2:126–139.
10. Doeffinger D, ed. The Kodak Workshop Series, Using Filters, 1988: 13, 45.
11. Sachdev VP, Radna RJ. Anterior-approach cervical discectomy under the operating microscope. Mt Sinai J Med 1994; 61:233–238.

The Prone-Oblique Surgical Position

Richard J. Radna, M.D., Ph.D., and Ved P. Sachdev, M.D.

Abstract

The prone-oblique surgical position as introduced and used by Dr. Malis at Mount Sinai Hospital is presented. The advantages of this position over the prone and knee-chest positions are noted. Recommendations for the safe use of the prone-oblique position are made. **Key Words:** surgical position, spinal surgery, suboccipital surgery.

Dr. Malis introduced the prone-oblique position at Mount Sinai Hospital for spinal surgery in 1975 (1) to diminish the potential complications of the prone and knee-chest positions. An optimal patient position for spinal surgery includes ease of positioning, adequate ventilation, low epidural venous pressure, good exposure of the interlaminar space, reduced risk of injury to prevertebral structures (1, 2), avoidance of postoperative pressure sores, and the comfort of the surgeon. The prone positions hold potential risks of neurological sequelae (3–6), hemodynamic problems (2, 7, 8), as well as local pressure complications (9, 10).

The prone-oblique position, or the three-quarter prone position, can be used for a variety of spinal and cranial approaches (1, 11, 12). Dr. Malis advocated the prone-oblique position because it provided access to the posterior and posterolateral aspects of the total spine, as well as the suboccipital region (1) (Figs. 1–4). The position is straightforward to use, gives excellent access for anesthesia to the airway (Fig. 2), enables the abdominal structures to fall away from the spine, with the abdomen totally free of pressure (Fig. 2), allows excellent flexion of the spine (Fig. 1), and provides a surgeon access to the surgical field, without flexing of the surgeon's back (Fig. 5), as required in the prone position.

Methods

The patient is placed on the operating table in the supine position. Anesthesia is induced, and the patient is intubated. The patient is then turned to the lateral position, and after preparation, hypodermic needles are placed in the region of the spinous processes at the surgical site. Radiographic verification of level is achieved with a lateral spine film. Marking of the level is achieved with a 0.3-cc injection of methylene blue dye. The patient is then turned to the prone-oblique position. With current microscope and head-mounted light delivery systems, which provide more than 10,000 foot-candles of light to the surgical field and have the capability of illuminating the undersurface of the surgical field (13), selection of whether the right or left side of the patient is up is a matter of the personal preference of the surgeon. The authors prefer right side up, as they are right-handed. For a unilateral, interlaminar approach, the up-side permits enhanced access to the interlaminar space, with increased flexion of the table.

Two axillary rolls are placed to protect the dependent brachial plexus and to diffuse uniform weight bearing to the shoulder, thoracolumbar region, and lower extremities. The axillary rolls can be constructed of sheets, foam bolsters, gel pillows, or intravenous (IV) bags surrounded by foam or sheepskin (Fig. 1). Sheepskin is used in some hospitals in which egg-crate foam is prohib-

---

From the Department of Neurosurgery, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029. Address reprint requests to Richard J. Radna, M.D., Ph.D., 1165 Park Avenue, New York, NY 10128.

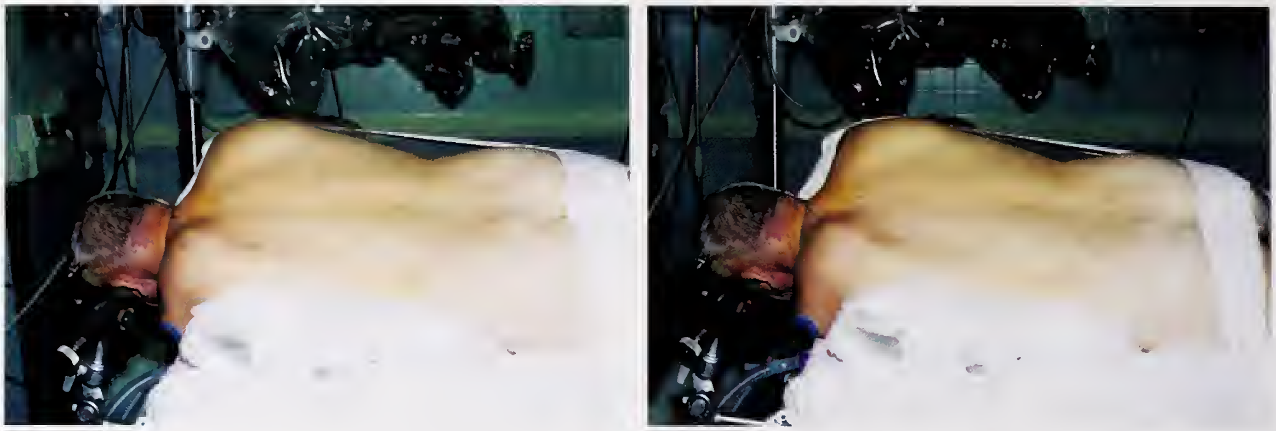


Fig. 1. Stereo posterior view of a patient in the prone-oblique position for a cervical decompressive laminotomy/facetectomy approach (15). The head is in a Gardner clamp. Note ready access from the suboccipital region continuously to the sacrum. Multiple bolsters support the entire thoracolumbar-dependent region for uniform weight distribution. Note the methylene blue mark at the C6 level, following injection into the region of the C6 spinous process.

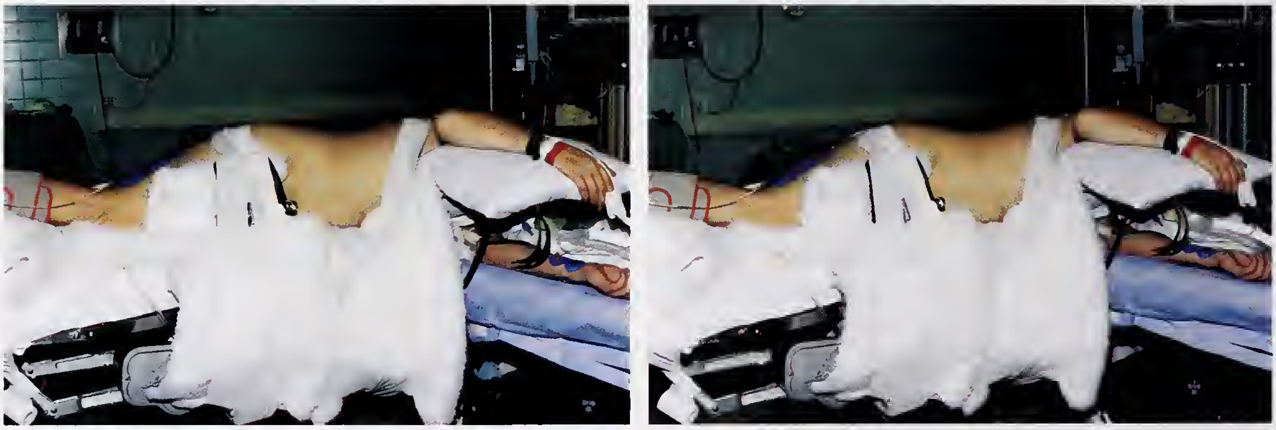


Fig. 2. Stereo anterior view of a patient in the prone-oblique position for a posterior lumbar interbody fusion. Note the kidney rest supporting the upper thigh, buttressed by a 1-L IV bag surrounded by sheepskin. The right arm is supported by a table-mounted arm support, also buttressed with a pillow, giving full access by the anesthesia staff to the airway. The abdomen is totally free. Intermittent compression stockings are in place. The portion of the operating table juxtaposed to the position of the scrub nurse is covered by foam and sheepskin to protect the nursing staff from bruising on table prominences.

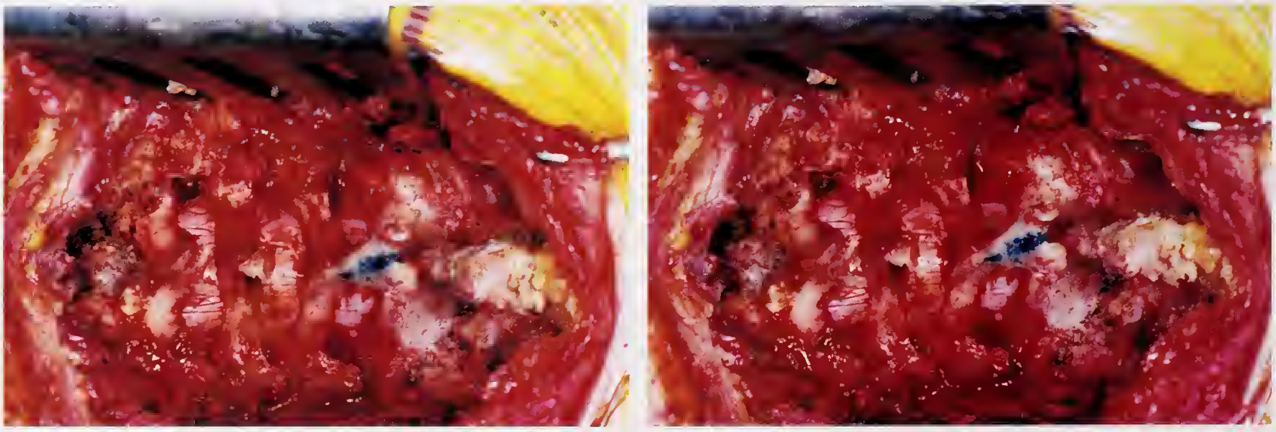


Fig. 3. Stereo surgical view of the bilateral cervical decompressive laminotomy/facetectomy approach of the patient shown positioned in Fig. 1. The right side of the patient is up. The methylene blue mark is at the C6 level, with decompression achieved at the C4/5, C5/6, and C6/7 levels. Retractors shown are a Taylor-Scoville, ebonized to diminish glare, and a Poppen-Gelpi.

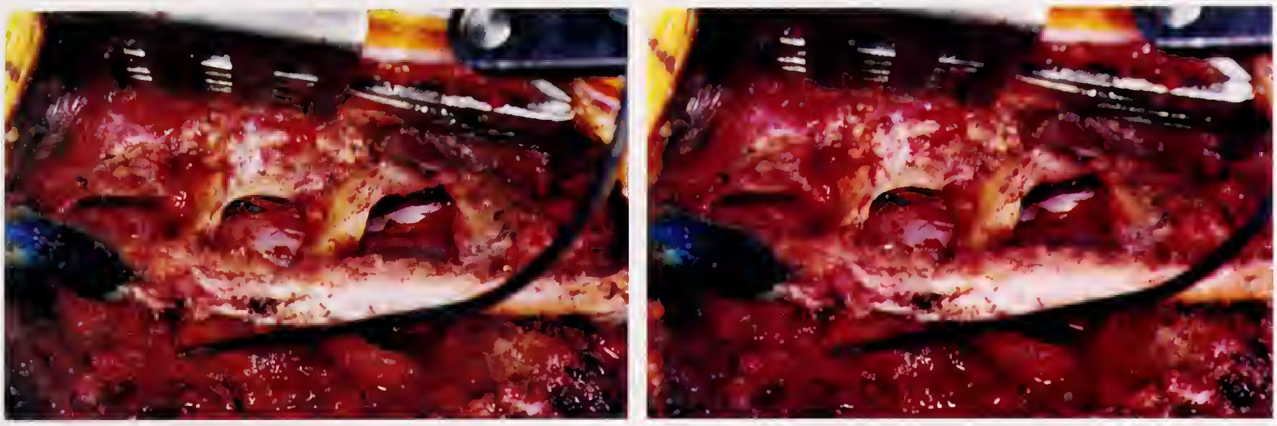


Fig. 4. Stereo surgical view of a bilateral lumbar decompressive laminotomy/facetectomy at the L3/4, L4/5, and L5/S1 levels (16). The right side of the patient is up. The L3 spinous process is marked with methylene blue dye. A Malis trans-spenoidal 7 Fr suction tip is shown on the left side. The retractor system shown is a Taylor-Scoville, which is enhanced by an auxiliary retractor system for the sacral paravertebral muscles (17).

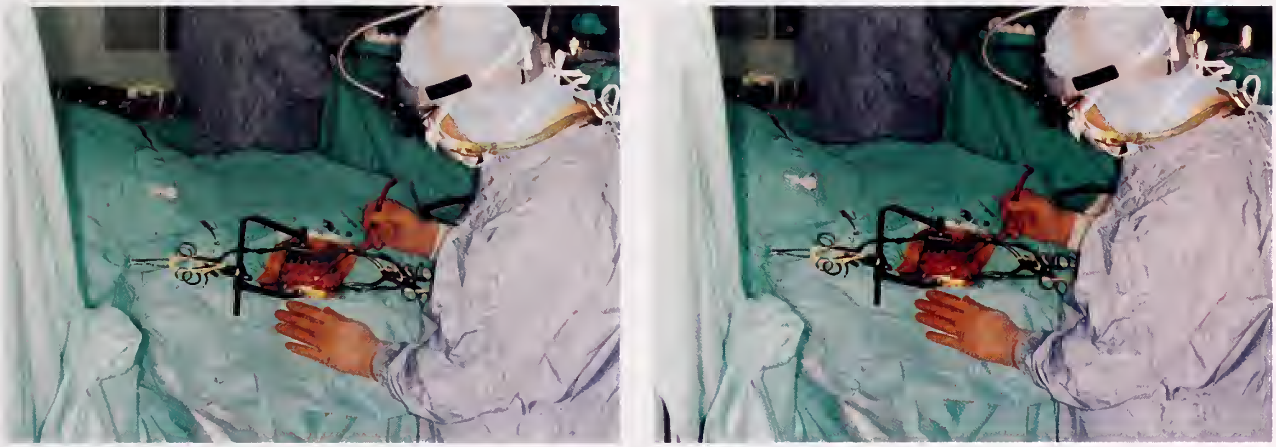


Fig. 5. Stereo surgical field view in a lumbar decompression approach, similar to the approach shown magnified in Fig. 4. The right side of the patient is up. Note the ready access the surgeon has to the surgical field, without bending over the patient for hours. More than likely, this will protect a surgeon who does lumbar laminectomies for 30 years from becoming the patient. All present in the operating room can have ready visibility of the surgical field without leaning over the surgical field; an optimal feature for resident and student teaching.

ited because of a reported fire hazard. The table is minimally flexed, with feet slightly elevated on pillows or bolsters. Any area not supported is buttressed by foam or sheepskin. In principle, aim is made to distribute support as uniformly as possible to diminish the possibility of pressure sores. For a relatively short procedure, such as a unilateral William's microdiscectomy, the table can be maximally flexed to open the unilateral interspace. For a longer or bilateral procedure, less table flexion is advisable to obviate focal pressure on the dependent thigh for any length of time. Spine flexion is achieved by placing the lumbosacral region on the surgeon's side of the operating table and by moving the patient's head and neck to the opposite side. We have found that lean, muscular patients are at greatest risk for pressure sores, which manifest themselves most severely as myonecrosis with myoglobinuria.

The upper thigh is supported by a kidney rest, which is fixed to the table and buttressed with foam or an IV bag surrounded with foam or sheepskin (Fig. 2). The upper arm is supported by pillows on a table-mounted arm support (Fig. 2). Care is taken that the upper leg is positioned so as not to put pressure on the dependent leg. The patient is secured to the table by tape and a strap fastener to safely allow side-to-side table movement during the operation. The portion of the table facing the scrub nurse can be covered with foam and sheepskin to protect the nurse from table prominences such as the kidney rest (Fig. 2).

Limitations of the Prone-Oblique Position

Any surgeon familiar with the prone-oblique position will bemoan the need to take an intraoperative film; only an oblique view is reasonably available. Radiographic level confirmation intraoperatively is much easier in the prone position. The authors do use the prone position on a radiolucent Wilson frame when placing spinal instrumentation because of the need for anteroposterior and lateral x-ray views. The difficulty in obtaining useful intraoperative x-rays in the prone-oblique position, can be avoided by marking films while the patient is lying laterally on the operating table before final positioning. This lateral view in the cervical region is facilitated by pulling down both shoulders during the x-ray while positioning the patient for the dependent shoulder and with tape for downward traction of the shoulder on the up-side.

The prone-oblique position also has the potential for pressure sores at the dependent axilla and thigh for long procedures, because weight is focused on these parts. This problem can be avoided by meticulous attention to the use of bolsters (Figs. 1 and 2) for distributing weight.

Results

Dr. Malis used the prone-oblique position exclusively for surgery of the thoracolumbar spine for 25 years, including resection of extensive intramedullary thoracolumbar spinal cord tumors, arteriovenous malformations of the cord, as well as management of radiculopathy. A lumbar decompression approach is shown in Fig. 4. A consecutive series of 300 lumbar disc cases operated on in the prone-oblique position, without significant complications related to positioning already appears in the microsurgical literature (14). The prone-oblique position has been used for suboccipital craniectomy and posterior cervical approaches (Fig. 3) in patients in whom the risk of air embolism, which is inherent in the use of the semisitting position, was particularly problematic. Dr. Malis preferred the semisitting position for posterior cervical and suboccipital surgery.

Conclusion

The prone-oblique surgical position, as used by Dr. Malis and those privileged to have trained with him, has been found to be a versatile, safe, and user-friendly position.

References

1. Malis LI. New trends in microsurgery and applied technology. In: Pluchino F, Broggi G; eds. Advanced Technology in Neurosurgery, Springer-Verlag, 1988.
2. Alexander JP. Problems associated with the use of the knee-chest position on lumbar intervertebral discs. J Bone Joint Surg 1973; 2:279–284.
3. Deem S, Shapiro HM, Marshall LF. Quadriplegia in a patient with cervical spondylosis after thoraco-lumbar surgery in the prone position. Anesthesiology 1991; 75: 527–528.
4. Langmayr JJ, Ortler M, Obwegeser A, Felber S. Quadriplegia after lumbar disc surgery: A case report. Spine 1996; 21:1932–1935.
5. Winter R, Munro M. Lingual and buccal nerve neuropathy in a patient in the prone position: A case report. Anesthesiology 1989; 71:452–454.
6. Kim C, Blank J, McClain BC. Transient paraparesis after general anesthesia in a patient in the prone position. Anesthesiology 1994; 81:775–777.
7. Yokoyama M, Ueda W, Yamamoto H. Hemodynamic effect of the prone position during anesthesia. Acta Anaesthesiol Scand 1991; 35:741–744.
8. Albin MS, Ritter RR, Pruett CE, Kalff K. Venous air embolism during lumbar laminectomy in the prone position: Report of three cases. Anesth Analg 1991; 73:346–349.
9. Anderton JM. The prone position for the surgical patient: A historical review of principles and hazards. Br J Anesth 1991; 67:452–463.
10. Ziser A, Friedhoff RJ, Rose SH. Prone position: Visceral hypoperfusion and rhabdomyolysis. Anesth Analg 1996; 82:412–415.
11. Benzel EC. The lateral extracavity approach to the spine using the three-quarter prone position. J Neurosurg 1989; 71:837–841.
12. Ausman JI, Malik GM, Dujovny M. Three-quarter prone approach to the pineal-tentorial region. Surg Neurol 1988; 29:298–306.
13. Radna RJ, Sachdev VP. Operative micro-photography: A Malis legacy. Mt Sinai J Med 1997; 64:207–212.
14. Sachdev VP. Micro-surgical lumbar discectomy: A personal series with at least 1 year of followup. Microsurgery 1987; 7:55–62.
15. Henderson CM, Hennessey RG, Shuey HM, Shackelford EG. Posterior-lateral foramenotomy as an exclusive operative technique for cervical radiculopathy: A review of 846 consecutively operated cases. Neurosurgery 1983; 13(5):504–512.
16. Aryanpur J, Ducker T. Multilevel lumbar laminotomies: An alternative to laminectomy in the treatment of lumbar stenosis. Neurosurgery 1990; 26(3):429–433.
17. Radna RJ. Auxiliary surgical retractor system. US patent 5,402,773. 1995 Apr 4.

A Biorbitofrontobasal Interhemispheric Approach for Suprasellar Lesions

KENJI OHATA M.D., AKIRA HAKUBA, M.D., D.M.SC., KENJI NAGAI, M.D., MICHIHARU MORINO, M.D., AND YOSHIYASU IWA

Abstract

Suprasellar tumors including pituitary adenomas and craniopharyngiomas, in the case of normofixed or postfixed chiasma and ruptured anterior communicating artery aneurysms in the acute stage, can be approached with minimum brain retraction, increased exposure, and safe manipulation in the shortest possible distance via a biorbitofrontobasal interhemispheric approach. Fourteen patients with pituitary adenomas, 3 with craniopharyngiomas, 7 with meningiomas, 2 with mucoceles, 1 with osteoma, and 3 with ruptured anterior communicating aneurysms in the acute stage were operated on, using this approach with excellent results. The operative technique and its results are detailed. **Key Words:** pituitary adenoma, craniopharyngioma, meningioma, communicating aneurysm.

Editor's note: Dr. Akira Hakuba took his early training in Osaka, Japan and then came to the United States. After an internship at the Cambridge City Hospital and a year of general surgery residency at the Buffalo General Hospital, he was accepted into neurosurgical training at the New England Medical Center by Tufts University School of Medicine. When Dr. Selverstone retired, Dr. Hakuba came to Mount Sinai Hospital in 1970 as a resident and fellow in microneurosurgery. When he returned to Japan in 1972, he was appointed Clinical Assistant at Osaka City University Medical School and then rose to Assistant Professor, Associate Professor, and finally Professor and Chairman in 1991. Dr. Hakuba has lectured and published extensively on skull base surgery and has designed microsurgical equipment. He has been Dr. Malis's host on numerous occasions, namely invitations to speak at various universities and neurosurgical societies in Japan.

LESIONS LOCATED HIGH in the suprasellar region are often difficult to approach because of both their deep position and their concealment by surrounding vital structures. Since 1982 we have used a biorbitofrontobasal interhemispheric approach consisting of a bifronto-orbital temporal craniotomy and separation of the olfactory nerves from the frontal lobes and opening of the interhemispheric fissure. This approach permits access straight upward to the suprasellar region and also downward into the sella turcica and safe manipulation of both suprasellar and intrasellar lesions via the shortest possible route.

Surgical Technique

The patient is placed in supine position. By using a Mayfield's three-pin headholder, the head is kept extended about 25 degrees at the craniovertebral junction. A bicoronal skin incision is made, starting at the superior margin of the right zygomatic arch about 1 cm anterior to the external auditory meatus, extended upward and slightly forward and medially, crossing the midline, and then slightly backward and downward running within the hairline to the level of the upper margin of the contralateral zygomatic

---

From the Department of Neurosurgery, Osaka City University Medical School, Osaka, Japan. Address reprint requests to Kenji Ohata, M.D., Department of Neurosurgery, Osaka City University Medical School, 1-5-7, Asahi-machi, Abeno-ku, Osaka 545, Japan.

arch. The skin flap is retracted anteriorly with the temporal fascia, which is separated from the temporal muscle on either side, and the frontal periosteum, which is elevated about 3 cm above the superior orbital margin. The superior and medial orbital margins are then exposed, maintaining continuity of the pericranium and the periorbit. The superior and medial periorbit is separated from the superior and medial walls of the orbit on either side. The frontal bone, nasion, and upper part of the nasal bones are exposed subperiosteally. The supraorbital nerve on either side is preserved by freeing it from the supraorbital canal, which is opened with either an air drill or a chisel, while protecting the periorbit with a periosteal elevator. Five burr holes are made (Fig. 1A): the first in the lateral frontal bone just behind the frontal process of the zygomatic bone, the second in the temporal bone 2 cm above the zygomatic arch, the third in the frontal bone about 5 cm above the upper margin of the orbit, the fourth in the frontal bone about 6 cm above the nasion in the midline on the right side, and the fifth in the lateral frontal bone just behind the frontal process of the zygomatic bone on the opposite side. Through the first and last burr holes in the frontal bone, multiple pieces of Gelfoam are inserted in the epidural space of the frontal

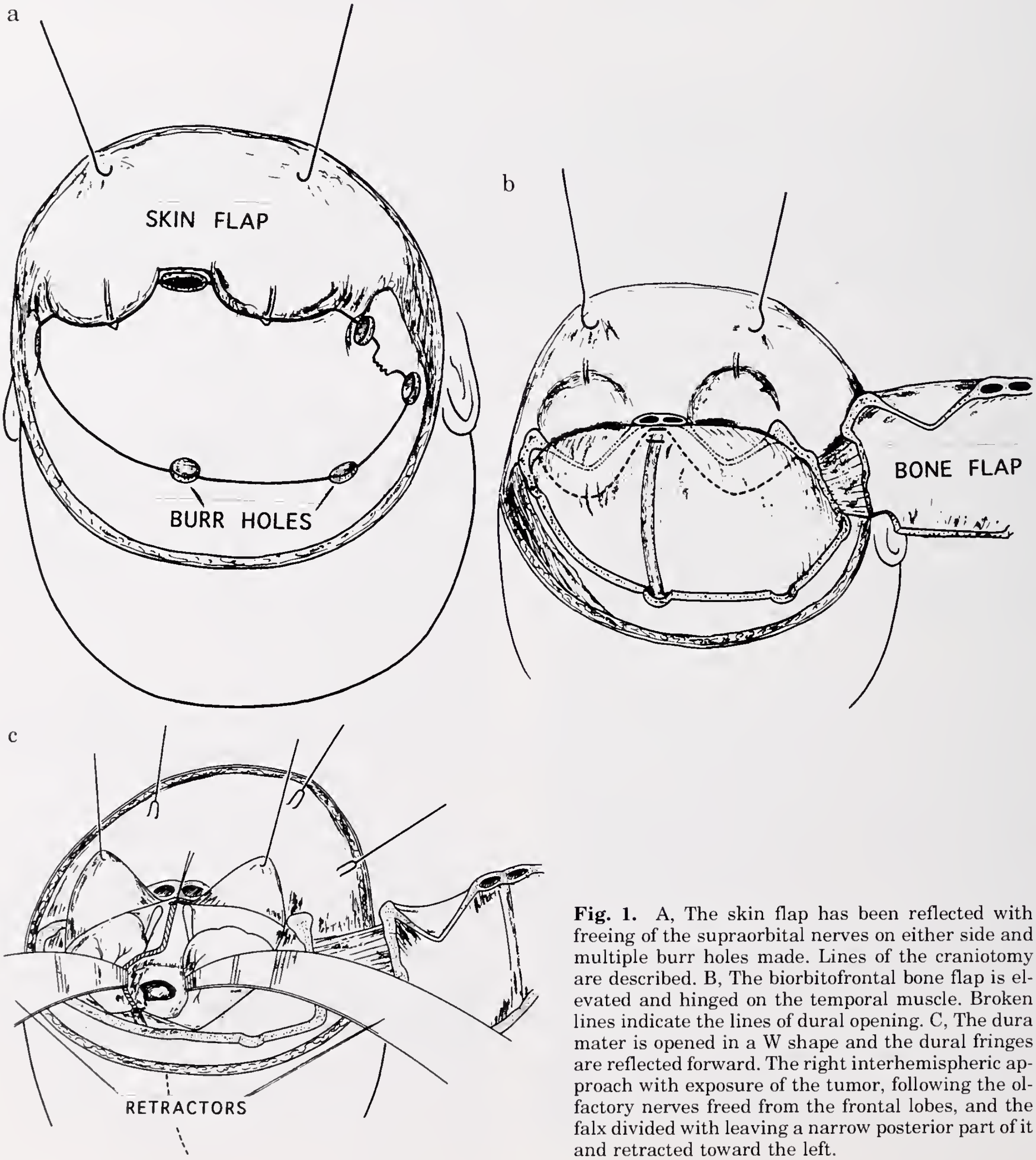


Fig. 1. A, The skin flap has been reflected with freeing of the supraorbital nerves on either side and multiple burr holes made. Lines of the craniotomy are described. B, The biorbitofrontal bone flap is elevated and hinged on the temporal muscle. Broken lines indicate the lines of dural opening. C, The dura mater is opened in a W shape and the dural fringes are reflected forward. The right interhemispheric approach with exposure of the tumor, following the olfactory nerves freed from the frontal lobes, and the falx divided with leaving a narrow posterior part of it and retracted toward the left.

base, and the dura mater of the anterior corner of the frontal base in the midline are carefully separated under the nasion on either side. An additional burr hole is made at the nasion by using an air drill. The roof of the orbit is divided, by using a sagittal saw and a thin chisel 5 mm wide, while protecting the periorbita with a periosteal elevator and the dura mater on the orbital roof with a Penfield's dissector; to divide the roof, a sagittal saw is inserted through the burr hole at the nasion, and is directed posterolaterally at about 45 degrees from the sagittal plane to make an approximately 3-cm cut in the medial orbital roof, and the lateral orbital roof is then divided through the burr hole in the frontal bone, right behind the zygomatic process, from the superior lateral corner of the orbit obliquely medialward to the point at which its path meets the above cutting line of the medial orbital roof from the nasion. The roof of the contralateral orbit is also divided in the same manner. The second and third burr holes, the third and fourth burr holes, and the fourth and fifth burr holes are then connected with a craniotome. The first and second burr holes are connected partially, by using a craniotome, to facilitate fracture of this portion of the bone. The bifrontoorbitotemporal bone flap is elevated and hinged on the right temporal muscle, which is retracted laterally (Fig. 1B). The mucosa of the frontal sinuses in the bone flap is completely removed. A sheet of the frontal periosteum slightly larger than the defects of the frontal sinuses is removed. Two frontal cortical bone pieces, about 1.5 mm in thickness, that are exactly the same shape and size as the bony defects of the frontal sinuses, are removed. The opened frontal sinuses are first covered by the above-described periosteum, the frontal cortical bone pieces are then wedged into the orifices of the sinuses and water-tight closure of the frontal sinuses is accomplished. With this procedure, sutures of the bone pieces to the bone edges of the opened frontal sinuses are not necessary. The dura mater is opened in semicircular fashion from the medial superior orbital margin to the lateral superior orbital margin on either side. The orbital contents are retracted downward by retracting the anterior dural fringes forward.

The operative microscope is then introduced and a subfrontal approach is taken with minimal retraction of the brain, and the right olfactory nerve is carefully dissected out from the base of the frontal lobe with sharp dissection nearly up to its origin in the olfactory trigonum and preserved on either side. The superior sagittal sinus is divided between two ligations very close to the frontal base from which the falx is divided almost completely, leaving its most posterior part 5 mm wide. Then the interhemispheric fissure on the right side is widely opened, with preservation of the multiple small vessels running in this fissure, with sharp dissection by using a diamond knife and a pair of scissors as well as an optoirrigator (Muranaka Co., Osaka, Japan). In approaching a large pituitary adenoma, the dome of the tumor can be visualized through this approach; the intrasellar part of the tumor can also be more easily visualized with minimal retraction of the frontal lobe because the angle of the operative field is very wide (Fig. 1C). Removal of the tumor is accomplished fairly well by using sharp and blunt dissection with a flat-knife, dull-ring curets and small rongeurs. Bleeding is well controlled by a Malis bipolar coagulator system with simultaneous irrigation and suction by the optoirrigator. The intrasellar portion of the tumor is removed by sharp dissection, suction, and curettage. The posterior half of the medial wall of the cavernous sinus, which can be visualized on either side, and the posterior half of the sellar floor and posterior wall of the sella turcica, which are also well visualized, are cleared of tumor under direct vision. The remaining anterior parts, which can be seen by passing a small mirror into the sellar turcica, are also removed completely. Bleeding from the cavernous sinus can be controlled simply by elevating the head of the table and alternative insertion of fibrinogen-soaked Gelform. The suprasellar portion of the tumor is decompressed internally. The arachnoid is dissected from the tumor capsule. The capsule is sharply dissected out from the optic chiasm and tracts and the elevated hypothalamus under direct vision. The pituitary stalk becomes visible as the size of the tumor is reduced (Fig. 2B). The flattened gland which is attached to the dome of the tumor can be localized by tracing it from the distal part of the pituitary stalk. The normal pituitary tissue can be preserved by removal of the tumor in the dome by gentle suction.

Summary of Cases

Since 1982 we have used this approach in 3 patients with large craniopharyngioma with a normofixed chiasm (Fig. 2, A–D), 14 with large pituitary adenomas, 7 with parasellar meningiomas, 2 with mucoceles, 1 with osteoma at suprasellar legion, and 3 with ruptured aneurysms of the anterior communicating artery in the acute stage; we obtained excellent results after radical

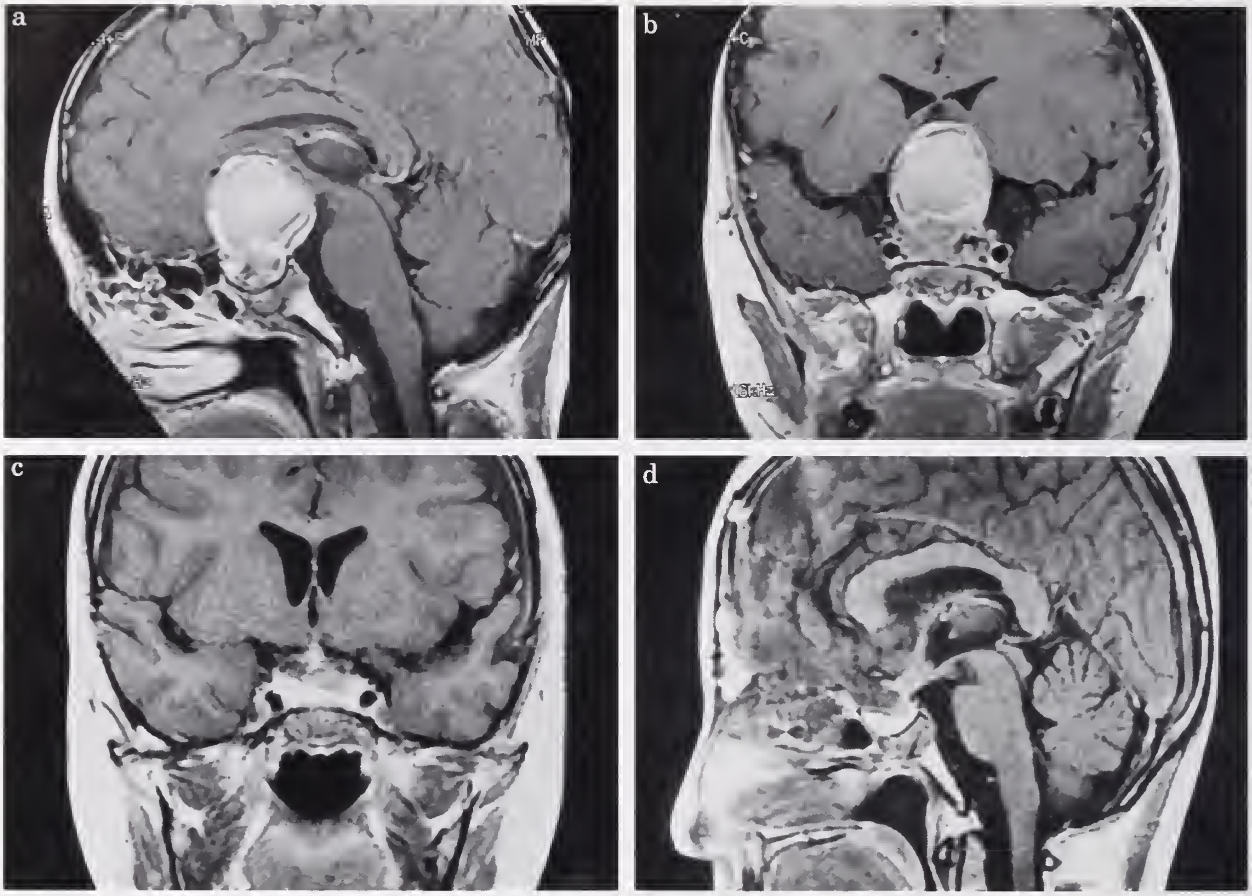


Fig. 2. A, B, Preoperative magnetic resonance imaging (MRI) in the case of a large craniopharyngioma (case 19, Table 1). C, D, The postoperative MRI demonstrates no usichial tumor. The pituitary stalk and gland have been preserved.

operations in all cases. Postoperative retraction hemorrhage was not encountered in any case. Fifty olfactory nerves were anatomically preserved in the 30 patients. Anosmia, however, was seen in 15 of these 30 patients. Visual functions were well preserved in all patients including those with pituitary adenomas, craniopharyngiomas, and meningiomas. Oculomotor and abducens palsies were seen in three and two patients, respectively, whereas trigeminal nerve deficit was found in one. These patients were completely recovered within 6 months after the operation. Postoperative swelling of the eyelids was a minor problem and usually subsided within 4 or 5 days. In all the 14 cases with pituitary adenomas, their pituitary function could be preserved and replacement therapy was not necessary.

Discussion

The biorbitofrontobasal interhemispheric approach offers a much wider working angle with minimal retraction of the frontal lobes than the usual subfrontal approach; therefore, dissection of the optic nerves, the anterior cerebral arteries and anterior communicating artery complex, and the superiorly displaced chiasm and hypothalamus can be performed more easily and safely under direct vision. The most posterior part of the falx is left intact while it is divided along the frontal base, because this will prevent the traction injury of the olfactory nerve during the manipulation of the frontal lobes.

To close the opened frontal sinus is much easier than in the usual bifrontal craniotomy because the remaining two cavities are very small. Despite the excellent results of Suzuki and Ito (1, 4) in the patients with aneurysms of the anterior communicating artery via a bifrontal interhemispheric approach and those of Ray (3) in the patients with pituitary adenomas via subfrontal approach, we feel that a biorbitofrontobasal interhemispheric approach will provide a better anatomic assessment of the lesions in the suprasellar region. An extensive frontobasal approach has been reported elsewhere (2), but it consists of an bifrontal craniotomy and an additional orbital osteotomy. Chance of postoperative infection may therefore be higher because of this free orbital bone flap. Our single osteoplastic bone flap hinged on the temporal muscle will provide less chance of postoperative infection and better cosmetic appearance of the face.

References

1. Ito Z. The microsurgical anterior interhemispheric approach suitably applied to ruptured aneurysms of the anterior communicating artery in the acute stage. Acta Neurochir 1982; 63:85–99.
2. Kawakami K, Yamanouchi Y, Kawamura Y, Matsumura H. Operative approach to the frontal skull base: Extensive transbasal approach. Neurosurgery 1991; 28:720–725.
3. Ray BS, Patterson RH. Surgical experience with chromophobe adenomas of the pituitary gland. J Neurosurg 1971; 34:726–729.
4. Suzuki J, Niizuma H. Surgical treatment of anterior communicating artery aneurysm (technical note). No Shinkei Geka [Neurol Surg (Tokyo)] 1981; 9:1009–1014.

Microneurosurgery in Suburbia

Martin H. Savitz, M.D.

Abstract

Private practice in the suburbs may be relaxed and filled with leisure time. There have been notable exceptions among the clinical professors at Mount Sinai. The principles of microneurosurgery include reviewing all neuroradiological studies to establish the diagnosis and planning the operative approach before entering the operating room, having adequate illumination and magnification, following anatomic planes without damage to neural elements, and not pursuing intraoperative exploration. During his tenure as Chairman of the Department of Neurosurgery at The Mount Sinai Medical Center, Dr. Malis raised an entire generation of neurosurgeons able to take its place in academia and/or suburbia.

Editor's note: When I applied for residency in December 1969, Professor Sidney W. Gross was Chief of Neurosurgery. Dr. Malis was one of my interviewers and emphasized that he would not be successor to Dr. Gross and that microneurosurgery was the entire future of operating safely on the brain and spinal cord. When I began my training in July 1970, I learned immediately that Dr. Malis would be the new chief and that he was associated with all the innovative microsurgical techniques in neurosurgery.

For some neurosurgeons, practice in the suburbs is far from the madding crowd of academia. Mentors in the Mount Sinai residency program managed teaching and research in complete balance with private practice. Full-time geographic educators were not the general rule.

My first rotation at Mount Sinai was on the Malis service, and on my first day I found myself assisting Dr. Malis during a microdiscectomy. The crouch position, the Zeiss operating microscope, and the bipolar coagulator all became instant parts of my residency training. The bipolar coagulator was referred to as "the bipolar" rather than "the Malis" even though the monopolar coagulator was regularly called "the Bovie." As he reached the closure of the wound, Dr. Malis allowed me to tie the sutures and immediately commented that I was using two-handed technique. "If I didn't tie with two hands at Boston City Hospital, my Harvard professor would rap me on the knuckles." "Neurosurgeons all use the one-hand technique." The next day he noticed that I was tying with one hand. "I didn't say that I didn't know how, but I valued my knuckles too much to offend my Harvard professor."

When I began my rotation as chief resident, Dr. Malis took me aside and informed me that I was quite slow in the operating room, in fact the slowest resident whom he had ever trained. My answer was that I never had a wound infection or a postoperative bleed caused by meticulous microsurgical technique. When I finished my residency, all he said was, "You're a little faster now." Since going into private practice my operating time has been one-half to one-third of all the other neurosurgeons at the various community hospitals where I have had privileges. I often jest that my attention span is quite short and that I have to finish before I forget what I am doing.

The true reasons have to do with the concepts of microneurosurgery. A one-hundred-thousand-dollar microscope and a complement of titanium instruments no more define a microsurgeon than a set of golden tools make an apprentice a craftsman. Before even scheduling an operative proce-

---

Address reprint requests to Martin H. Savitz, M.D., 55 Old Turnpike Road, No. 101, Nanuet, NY 10954.

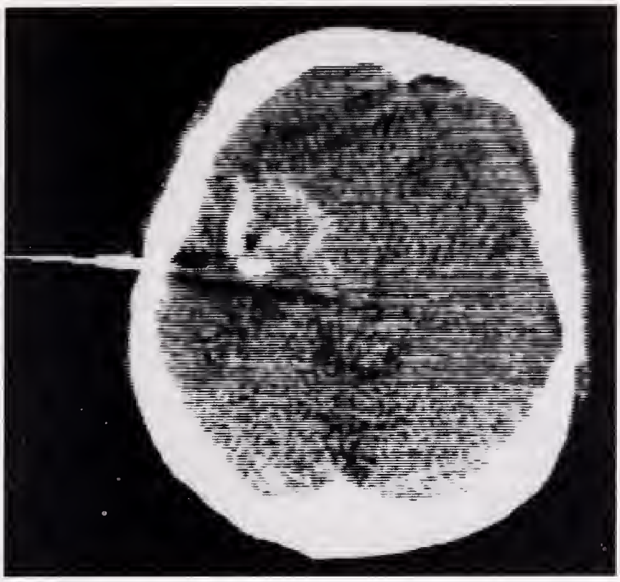


Fig. 1 The low density of air shadow within tumor identifies area of biopsy.

dure, the neuroradiological studies should have established the diagnosis, dictated the operative approach, and eliminated any need for intraoperative exploration.

While still a resident, I asked Dr. Malis about needle procedures on the brain and was told that blind puncturing of the cortex and white matter was contrary to the microsurgical principles of following anatomic planes under good illumination and magnification and was improper for any neurosurgeon from Boston (my birth place). As soon as I was established in Rockland County, 30 neurological specialists including myself bought the thirteenth CT scanner in the United States. A visit to the Karolinska Institute allowed me to observe stereotaxis and the first attempt to apply a frame for CT-guided needling of the brain. The neuroradiologists in Stockholm taught me that a CT scanner was in fact a stereoscopic machine and that free-hand technique with CT guidance would allow safe and accurate biopsy and drainage of intracerebral lesions (1). Dr. Malis then allowed the innovation at The Mount Sinai Hospital; he was never against proven neurosurgical innovation.

One of the earliest CT images (Fig. 1) allowed localization and accurate biopsy of tumors with a Lee-Field guillotine needle. Drainage of cerebral abscesses with a 13-gauge needle did not require further neurosurgical intervention in most cases because of the development of third-generation antibiotics which penetrated the blood-brain barrier and eradicated the infection. Treatment of intracerebral hematomas by a CT-guided Cone needle was more controversial because successful therapy depended on the control of hypertension; most of the cases of spontaneous hemorrhage underwent a second drainage to completely remove residual liquid clot.

The neuroradiological evaluation of spinal stenosis, spondylosis, and disk herniation has been in a constant state of evolution and reevaluation. The dilemma still arises as to whether to use CT, myelography, CT-myelography, or magnetic resonance imaging (MRI). CT-myelography has been considered the gold standard but the method is invasive, requires the intrathecal injection of contrast media, and uses ionizing radiation. There has also been the known morbidity of cephalgia, seizures, and late arachnoiditis (2). MRI was available in Rockland County 3 years before the Mount Sinai Medical Center acquired the innovative technology. Spinal surgery following CT and MRI and without myelography has been my custom for more than 15 years (3).

After studying with Dr. Malis at Mount Sinai, Williams (4) presented his original concepts of microlumbar discectomy: 1) preoperative x-ray localization with as small a skin incision as possible; 2) the magnification and illumination provided by the operating microscope; 3) no alteration of the lamina or facet joint; 4) no coagulation or removal of fat within the epidural space; and 5) removal of a minimal volume of disc material without incision of the annulus or curettage. Subsequent clinical investigation concluded that each of these principles alone might be responsible for results superior to standard laminectomy. Multiple requests by patients for microdiscectomy prompted me to adopt minilaminotomy (Fig. 2).

Williams had unique motivation to develop the technique of minilaminotomy, namely Las Vegas showgirls, who could not display more than a one-inch incision or stay out of work more than 2 weeks. The term "minilaminotomy" (5) was coined to describe microsurgical techniques which not only relieved segmental spondylosis and lateral recess syndrome but also provided adequate exposure of sequestered fragments without excessive nerve root retraction. No attempt was made to avoid removal of bone or ligamentum flavum. Standard Kerrison punches were not abandoned in favor of a high-speed drill. As for the epidural fat and veins, hemostasis and clear inspection of the posterior longitudinal ligament were the prime considerations. Because ordinary instruments were used, a fiberoptic headlight and binocular loupes were the only other equipment needed. Even as a fully trained microneurosurgeon, I preferred the speed and ease of using a

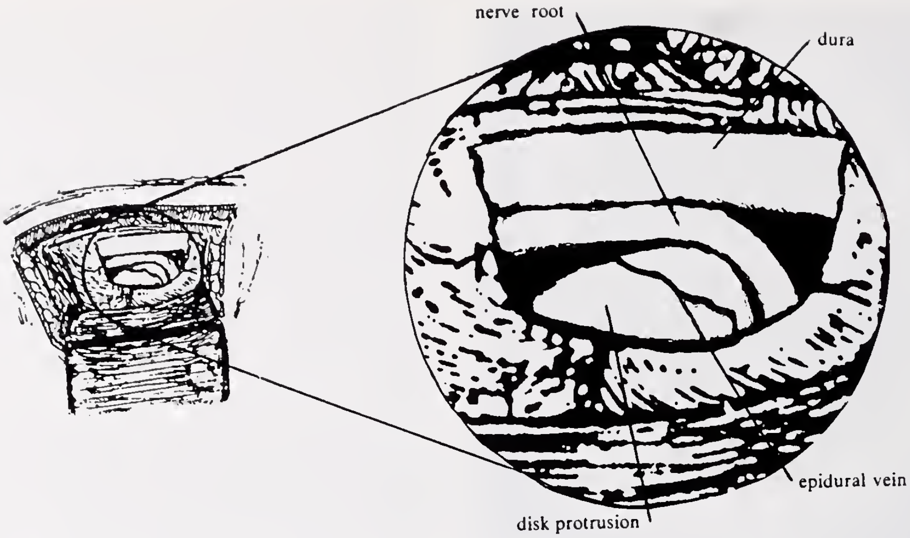


Fig. 2 Artist's drawing of minilaminotomy incision with surgeon's view magnified 4.5× by binocular loupes.

coaxial beam of cold light with 4.5× magnification. The size of the surgical wound, dimensions of the bone opening, quantity of disk material excised, and amount of perineural fat preserved are not as important as the skill of the surgeon, correlation of neuroradiological images with clinical findings, patient selection, and avoidance of complications.

While the author was in residency training from 1970 to 1974, either the operating microscope or 4.5× binocular loupes were used in every anterior cervical discectomy (Fig. 3). The "sandwich" bone graft was obtained from the iliac crest. In 1975, Hankinson and Wilson (6) reported anterior cervical discectomy with the operating microscope but without fusion. The results without a graft were comparable with Cloward (7) and Robinson and Smith (8): negligible blood loss, little tissue swelling, less narcotic requirement, fewer days in the hospital, earlier return to normal activity, no wound infection or discitis, and low rate of reoperation. The minimalist approach (8) should be easily mastered by neurosurgeons performing standard anterior cervical discectomy and fusion for a herniated cervical disk. Other than a small number of Cloward instruments, a power drill, fiberoptic headlight, and binocular loupes are the only other equipment needed for discectomy and removal of osteophytic ridges.

Elaborate methods of assessing the results of disk surgery have been described. Questionnaires, psychological testing, serial neurological examination, the bias of compensation cases, electromyographic testing, and computer analysis have all been applied. My own way was quite direct, simply allowing the patient to judge. About

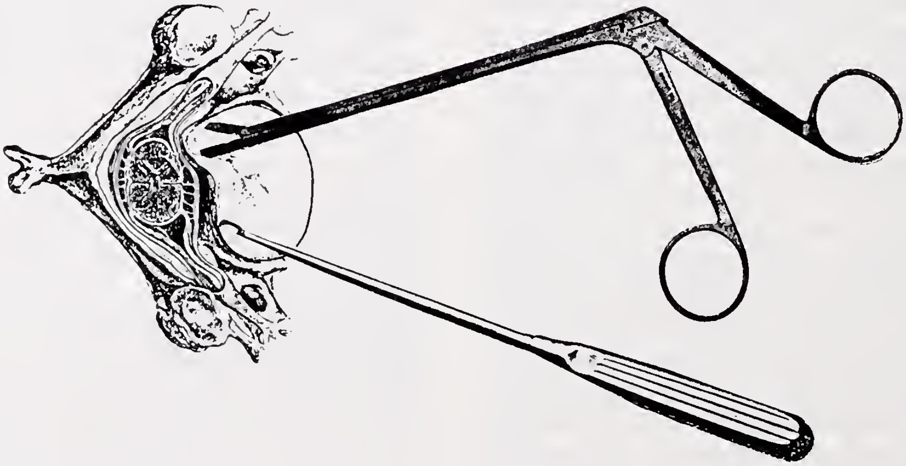


Fig. 3 Axial view of Cloward forceps and microcurettes within a disk space containing a herniated nucleus pulposus.

90 to 95% replied affirmatively, and 5 to 10% said, "No." Operations requiring 60 minutes or less are associated with very low rates of postoperative complications, and I have never had to leave my house nights or weekends for any elective case.

Research in the suburbs may encounter resistance to acceptance for publication. Many editors do not think that clinical investigation should take place in bucolic babel away from the surveillance of full-time professors at university hospitals. Before submitting a manuscript, I availed myself of every opportunity to present papers at local, regional, national, and international meetings. The informal comments and questions of neurosurgical colleagues helped refine the manuscripts before they were subjected to the actual peer review process employed by the various surgical journals. There are now 75 entries on my bibliography. Dr. Malis allowed my first clinical investigation on his private patients in my first year of residency and enabled me to complete 10 journal articles by the completion of my training. Always willing to review original work, provide suggestions, and edit texts, Dr. Malis raised an entire generation of neurosurgeons able to take their place in academia and suburbia.

References

1. Savitz MH. Free-hand CT-guided needle for biopsy and drainage of intracerebral lesions. Ten years experience. Surg 1992; 77:211–215.
2. Savitz MH, Katz SS, Zablow BJ. Discectomy following CT and MRI and without myelography. Mt Sinai J Med 1988; 55:162–166.
3. Savitz MH. Spinal surgery following computerized tomography (CT) magnetic resonance imaging (MRI) and without myelography: 10 years experience, J Neurol Orthop Med Surg 1996; 17:35–45.
4. Williams RW. Microlumbar discectomy: A conservative surgical approach to the virgin herniated lumbar disc. Spine 1978; 3:175–182.
5. Savitz MH. Minilaminotomy as an alternative to laminectomy or microdiscectomy: Ten years' experience, Mt Sinai J Med 1986; 58:165–167.
6. Hankinson HI, Wilson CB. Use of the operating microscope in anterior cervical discectomy without fusion. J Neurosurg 1975; 43:452–456.
7. Cloward RB. The anterior approach for removal of ruptured cervical discs. J Neurosurg 1958; 15:602–617.
8. Robinson RA, Smith GW. Anterolateral cervical disc removal and interbody fusion for cervical disc syndrome. Bull Johns Hopkins Hosp 1955; 96:223–224.
9. Savitz MH. Minimalist approach to anterior cervical discectomy. Mt Sinai J Med 1994; 61:239–242.

Radiologic Evaluation in Patients with Head Injury

MICHAEL H. BRISMAN, M.D., AND MARTIN B. CAMINS, M.D.

Abstract

Head injury is common. With many excellent imaging techniques readily available, radiologic evaluation has become critical in the management of patients with head injuries. We review the indications for various imaging studies in patients with head injury. In general, a noncontrast computed tomography of the head is the study of choice for patients with head injury and should be performed whenever there is reasonable suspicion of a serious injury to the brain. **Key Words:** radiology, head injury, CT scan.

Editor's note: After his premedical education at Harvard College and medical school at Columbia University, Dr. Brisman is currently a neurosurgical resident at The Mount Sinai Hospital. Dr. Camins underwent training in neurology from 1970 to 1971 and training in neurosurgery from 1971 to 1975 at the Neurological Institute of New York Columbia-Presbyterian Medical Center; his current academic appointment is Associate Clinical Professor of Neurosurgery at the Mount Sinai School of Medicine.

THE INCIDENCE OF TRAUMATIC BRAIN injury in the United States has been estimated at 200 per 100,000 people per year, that is, about 500,000 injuries per year. Each year in the United States, head injuries cause 100,000 deaths and new permanent disabilities in about 75,000 people. Furthermore, people with significant head trauma often have associated significant systemic injuries. The most common cause of head trauma is motor vehicle accidents.

In discussing proper radiologic evaluation of patients with head injury, we will cover the following topics: (a) what treatable pathology is being sought, (b) how are head injury patients evaluated clinically, (c) what radiologic tests are available, (d) what recommendations for radiologic studies are made in the literature, (e) what is the cost effectiveness of various radiologic studies in patients with head injury, and (f) what are our current recommendations for radiologic evaluation of patients with head injury.

Treatable Pathology

In considering which radiologic studies to pursue in patients with head injury, we must first consider what treatable lesions we are looking for. These fall into five main categories: (a) open penetrating injury to the brain, (b) intracranial hemorrhage, (c) cerebral edema, (d) cerebrospinal fluid leak, and (e) cervical spine injury.

Patients with open penetrating brain injuries including open depressed skull fractures and gunshot wounds are at increased risk of meningitis and will benefit from early intraoperative debridement and dural repair.

Patients with intracranial hemorrhage will benefit from emergent surgical evacuation if there is an epidural or subdural hematoma which is more than several millimeters in size. Some patients with supratentorial intracerebral hemorrhage may benefit from surgical evacuation as well, particularly if the hemorrhage is large and

---

Address reprint requests to Michael H. Brisman, M.D., Department of Neurosurgery, Box 1136, Mount Sinai School of Medicine, One Gustave Levy Place, New York, NY 10029.

TABLE 1
Glasgow Coma Scale

Motor		Verbal		Eye Opening	
Obeys commands	6				
Localizes pain	5	Oriented	5		
Withdrawal to pain	4	Confused	4	Spontaneous	4
Decorticate posture	3	Inappropriate	3	To voice	3
Decerebrate posture	2	Incomprehensible	2	To pain	2
No movement	1	None	1	None	1

causing significant mass effect, although the benefits of surgery in these cases are somewhat controversial. Intraventricular hemorrhage can cause obstructive hydrocephalus which can be treated with ventricular drainage (ventriculostomy). Subarachnoid hemorrhage, particularly in patients with more severe head injury, can cause vasospasm of cerebral arteries and subsequent cerebral ischemia. The vasospasm and resultant cerebral ischemia may be relieved with nimodipine, a calcium channel blocker (1). Patients with intracranial hemorrhage should have aggressive correction of any coagulopathy (elevated prothrombin or partial thromboplastin times, or decreased platelet count) because coagulopathy in these patients is significantly associated with increased likelihood of further hemorrhage (2). Finally, the risk of seizures within the first week after head injury can be reduced in patients with intracerebral hemorrhage or poor neurological condition (Glasgow Coma Scale < 10) with the use of phenytoin (3).

Cerebral edema occurs with more severe head injury and, like intracerebral hemorrhage, can cause elevated intracranial pressure and injury to important brain structures, particularly the brainstem. Elevated intracranial pressure can be managed with various measures including surgical evacuation of mass lesions, hyperventilation (only used in the acute phase for cerebral herniation), intravenous mannitol, ventricular drainage, and pressor agents which can help maintain adequate cerebral perfusion pressures. The benefits of barbiturates and lobectomy for management of intractable intracranial hypertension is controversial.

Brain injury also occurs with skull fractures which can cause communication of intradural spaces with nonsterile, extracranial spaces which is manifested by a cerebrospinal fluid leak (otorrhea or rhinorrhea). Post-traumatic cerebrospinal fluid leak is first managed conservatively, but if it is persistent, may require spinal fluid drainage (via a lumbar spinal drain) or surgical repair.

Finally, it is important to remember that injury to the head, particularly an axial load injury to the vertex, can cause treatable injuries to the cervical spine and spinal cord. Such injuries can include unstable fractures which can be treated with open or closed reductions and internal or external stabilizations, epidural spinal hematomas which can be surgically evacuated, and spinal cord injury which can be minimized with a 24-hour regimen of mega-dose methylprednisolone (solumedrol) (4).

Clinical Evaluation

In discussing patients with head injury, it is important to establish a consistent system of clinical neurological evaluation. There are two such systems which are usually used. The first is the Glasgow Coma Scale (GCS) (Table 1) in which patients are scored from 3 to 15 on the basis of best motor response, verbal response, and eye opening. The second major system of evaluation divides patients into three categories of risk for serious brain injury on the basis of the history and physical examination (Table 2) (5).

Also critical in the evaluation of patients with head trauma is pupil size and reactivity, because a relatively large, unreactive pupil is very suggestive of ipsilateral uncal herniation with compression of the third cranial nerve. Patients with head injury may have signs of a skull base fracture including periorbital ecchymosis (raccoon eyes), ecchymosis behind the mastoids (Battle's sign), a seventh or eighth cranial nerve palsy from injury within the temporal bone, bleeding from the nose or ears, or a cerebrospinal fluid leak (otorrhea or rhinorrhea). Patients with a significant head injury may also have signs of elevated intracranial pressure (ICP), which can include bradycardia, hypertension, and respiratory irregularities (Cushing's triad), or a sixth nerve palsy. Finally, a hemiparesis is very suggestive of a contralateral cerebral hemorrhage.

Radiologic Imaging Techniques

Skull X-ray

The least expensive and most readily available test, the skull x-ray, can demonstrate skull fractures but does not give any information about the status of intracranial contents.

Computed Tomography (CT)

The scan is of intermediate expense and is readily available at all major trauma centers. It is

TABLE 2
Risk of Serious Brain Injury

Low Risk	Moderate Risk	High Risk
Asymptomatic	Loss of consciousness	Depressed consciousness[a]
Headache	Progressive headache	Focal neurologic signs
Dizziness	Alcohol or drug intoxication	Penetrating skull injury
Scalp hematoma	Age under 2 years[b]	Palpable depressed fracture
Scalp laceration	Post-traumatic seizure	Decreasing consciousness level
Scalp contusion	Vomiting	
Scalp abrasion	Suspected child abuse	
No moderate-risk criteria	Post-traumatic amnesia	
No high-risk criteria	Multiple trauma	
	Serious facial injury	
	Signs of basilar skull fracture	
	Possible skull penetration	
	Possible depressed fracture	
	Unreliable history of injury	

[a] Not clearly related to alcohol, drugs, seizure, or other metabolic cause.
[b] Unless injury very trivial.
Source: Reference 5.

the study of choice for evaluating the extent of acute hemorrhage and skull fractures, which are the most important considerations for acute neurosurgical intervention.

Magnetic Resonance Imaging Scan

The magnetic resonance imaging (MRI) scan is the most expensive test, it gives the best definition of brain structures, and allows for sagittal imaging. This study can take almost an hour to perform and is often not readily available. It is not as good as the CT scan for evaluating subarachnoid hemorrhage or skull fractures (6, 7).

Recommendations for Imaging in Patients with Head Trauma—A Literature Review

Several studies have investigated the utility of the skull x-ray in the evaluation of patients with head injury. One of the most important of these studies was a multidisciplinary panel study by Masters et al. (5). They found that none of the "low-risk" patients had an intracranial injury, 4% of the "moderate-risk" patients had an intracranial injury, and 29% of the "high-risk" patients had an intracranial injury. Although the presence of a skull fracture did markedly increase the likelihood of an intracranial injury in the moderate and high-risk groups, there was still a large percentage of patients with normal skull x-rays who had an intracranial injury; 7 of 10 moderate-risk patients with intracranial injury had a normal skull x-ray and 7 of 24 high-risk patients with intracranial injury had a normal skull x-ray. They concluded that low-risk patients do not need radiographic studies and that high-risk patients need CT scanning. For moderate-risk patients they concluded that CT scanning should be considered and that skull x-rays might be helpful if they showed abnormal results, but that a normal skull x-ray in this setting did not rule out intracranial pathology. When three other large studies from the literature were also considered (8–10), none of 9,765 low-risk patients had an intracranial injury.

Another more recent study (11) has also confirmed that many patients with intracranial injury will have normal skull x-rays. This study found that of 566 patients with GCS 13–15 after head injury, 19 patients developed intracranial injury of which 11 had no fracture on the skull x-ray. This study and another study of 373 patients (12) concluded that skull x-rays were of no benefit in head-injured patients with GCS of 13–15.

CT scan, because of its ability to assess intracranial pathology, has been used frequently in the management of patients with head injury. There have been several studies performed which have tried to assess which patients should receive a head CT after trauma.

It is generally agreed that patients in the low-risk category do not require head CT or skull x-ray because there is essentially no risk of intracranial injury. It is also generally agreed that patients in the high-risk category do require a head CT because the likelihood of intracranial injury is quite substantial [29% in the study by Masters et. al. (5)] Now that CT scanners are so quick and readily available, it is extremely rare that a neurosurgeon will operate on a high-risk patient before first obtaining a head CT. It is in the moderate-risk group of patients that CT scanning is somewhat more controversial.

There is some question in the literature regarding management for patients with head trauma with a GCS 13 or 14. By definition, these are patients who, at the very least, are lethargic (not spontaneously opening eyes), confused/disoriented, or not following commands. Mohanty et al. (13) concluded that such patients can be managed without a head CT. This study reviewed 348 patients with GCS 13–15 who were older than 18 years, had no clinical evidence of a skull base fracture, and were neurologically stable for at least 20 minutes after arrival in the emergency room. The vast majority of patients included in the study had GCS 14 or 15. Only 12 of the 348 patients (3%) had intracranial pathology, and none required surgical intervention.

Many studies, however, have demonstrated significantly higher rates of intracranial injury in patients with GCS 13 and 14 and thus have recommended head CT for such patients. Harad and Kerstein (14) reported on patients with GCS 13–15 who also had at least one of the following risks factors: loss of consciousness, amnesia, focal deficit, depressed or open skull fracture, deteriorating mental status, or pupillary inequality. They found that 3 of 11 patients with GCS 13 (27%), 9 of 40 patients with GCS 14 (23%), and 43 of 251 patients with GCS 15 (17%) had intracranial pathology, and that a total of 4% of the patients required a neurosurgical procedure.

Feuerman et al. (12) retrospectively reviewed 373 patients with head trauma older than 16 years who were admitted with a GCS 13–15. Of the 21 patients with GCS 13 who underwent head CT, 13 (62%) demonstrated intracranial pathology, although none required an operation. Of the 49 patients with GCS 14 who underwent head CT, 20 (41%) demonstrated intracranial pathology, and 3 patients had an operative hematoma. Of the 59 patients with GCS 15 who underwent head CT, 20 (34%) had intracranial pathology and 2 patients had an operative hematoma.

Schynoll et al. (15) also found that a GCS < 15 was a significant predictor of intracranial pathology. Their review included 31 patients with GCS 13 or 14 who had sustained nonpenetrating head trauma and, of these, 9 (29%) were found to have intracranial pathology on head CT.

Most controversy over management of head trauma arises when the GCS is 15 and the patients fall into the moderate-risk category by virtue of one of the previously mentioned criteria, most notably, loss of consciousness or amnesia for the traumatic event. As mentioned previously, Mohanty et al. (13), in their review of head trauma patients with a GCS 13–15, had found that only 3% of patients had intracranial pathology and none required an operation; on this basis they recommended admission without head CT for these patients.

Masters et al. (5) had found a 4% risk of intracranial pathology in patients with head trauma in the moderate-risk category, and suggested that these patients should receive "extended close observation" to watch for high-risk signs and that a head CT could be considered. They also concluded that a skull x-ray, if positive, may rarely be helpful; but if normal, it did not rule out intracranial pathology.

On the other hand, other investigators have found higher rates of intracranial pathology in patients at moderate risk with GCS 15 and have suggested that all such patients receive a head CT. For example, Harad and Kerstein (14) found a 17% rate of intracranial pathology in such patients. Stein et al. (16) found an 11% rate of intracranial pathology in such patients and also advocated head CT for all such patients.

Jeret et al. (17) reviewed 712 patients with nonpenetrating head trauma who had loss of consciousness or amnesia and GCS 15. They found that 9.4% had intracranial pathology. However, because only two (0.3%) patients required an operation, they felt it was unclear whether these patients should routinely undergo head CT.

Miller et al. (18) reviewed 1382 patients with a GCS of 15 and either loss of consciousness or amnesia for the event. They found that 84 (6.1%) patients had an intracranial abnormality, but that only 3 (0.2%) required an operation. However, of the subgroup of 789 patients with no signs or symptoms of depressed skull fracture, only 24 (3%) had an intracranial abnormality, and none required surgery. On this basis they concluded that for patients with GCS 15 and loss of consciousness or amnesia, routine head CT was not warranted unless the patient also had signs or symptoms of depressed skull fracture.

There are some studies that have reviewed the value of MRI for patients with head injury (6, 7, 19). The disadvantages of MRI in the setting of trauma are its limited availability, cost, the increased time needed to complete the study, and the difficulty in managing seriously ill patients in MRI machines, particularly patients on ventilators. Furthermore, MRI provides poorer evaluation of fractures and subarchnoid hemorrhage compared with CT. It has been suggested that

MRI may better assess subacute hemorrhagic lesions and may thus be more useful than CT in the evaluation of child abuse (7, 19). Another study has demonstrated that the MRI is somewhat more sensitive in detecting shearing injuries, small hematomas, and contusions than CT (6). However, this same study showed that in a series of 107 patients with head trauma, acute intervention was not altered in even a single case on the basis of the MRI.

Finally, it is very important to remember that an isolated injury to the head can produce serious injuries to the cervical spine. The cervical spine x-ray remains the gold standard screening study for the evaluation of cervical spine fractures and dislocations. A cervical spine series should consist of a lateral view down to the C7/T1 junction as well as an AP and open mouth view, and should be performed in any trauma patient with neck pain or tenderness, or an abnormal neurological examination. CT, myelogram, or MRI may be useful adjunctive imaging tests if the x-ray or neurological examination suggest a cervical spine or spinal cord injury.

Cost Effectiveness of Radiologic Studies in Patients with Head Trauma

Since resources are limited, monetary costs of various tests and procedures need to be considered to maximize effective patient care. The application of this concept in head trauma is that patients should undergo radiologic imaging only if there is some reasonable chance that it will alter treatment or avoid other costs that would otherwise be incurred, such as the cost of hospital admission.

For example, patients with head trauma who fall in the low-risk category have almost no chance of having intracranial pathology and therefore imaging studies in these patients for "defensive" purposes is a very poor use of resources. In 1994 the Office of Technology Assessment of the U.S. Congress computed the estimated annual cost of selected diagnostic radiographic procedures for head injury in persons 5 to 24 years old (20). The total annual cost of defensive radiology was more than 44 million dollars. This included 4 million dollars for defensive skull x-rays, 4 million dollars for defensive cervical spine radiographs, and 36 million dollars for defensive CT scans, but this study did not include the cost of MRI examinations. This study probably underestimated the overall cost ascribed to defensive medicine because costs applicable to private insurance were derived from Medicare data.

Patients with head trauma with GCS 12 or less are at significant risk of intracranial injury and should clearly receive emergency head CT. Without such imaging these patients would clearly receive inadequate care and there would be significant increased costs for delayed diagnosis of serious intracranial lesions in terms of additional medical and rehabilitational care for these patients, lost work time, as well as large malpractice costs.

Most studies have suggested that patients with GCS 13–14 are also at considerable risk for intracranial injury and thus cannot be cared for adequately and efficiently without a head CT. There is some disagreement on this point, as mentioned previously.

The cost-benefit analysis for patients with GCS 15 with a moderate-risk feature such as loss of consciousness or amnesia is the most difficult. Those who argue against obtaining a head CT in these patients point out the low percentage of such patients who will require a neurosurgical operation, which may be approximately 0.2% (18) or 0.3% (17).

Those who argue in favor of obtaining a head CT in these patients point out that there are clearly patients in this category who will require emergency neurosurgery and that, although surgical lesions may be infrequent, intracranial pathology that can potentially be treated with nonsurgical methods is not so uncommon: 6–17% depending on the series (14, 16–18). Furthermore the medical and legal costs of missing the diagnosis in even a small but definite number of patients may outweigh the monetary benefits of not performing a screening head CT in these patients.

A final consideration in this argument is that performing a screening head CT in these patients avoids the costs of a hospital admission, which is usually at least as costly as the CT scan itself. This argument is supported by such studies as that of Stein and Ross (21)—of 542 patients with GCS 13–15 with loss of consciousness or amnesia who had a normal head CT, none subsequently had any clinical deterioration—and of Davis et al. (22)—of 400 children with GCS 13–15 and normal head CT all did well, and only four required readmission to the hospital (2 for concussive symptoms, 1 for a symptomatic contusion treated with observation only, and 1 for a symptomatic subdural hematoma in a patient on coumadin which required neurosurgical drainage).

Stein et al. (16) used their own data to perform a detailed cost analysis for imaging in patients who had head trauma with GCS 14–15 with loss of consciousness or amnesia, considering the following three treatment options: (a) skull x-ray and admission for all patients, with CT scan only for patients with a skull fracture or neurological deterioration, (b) CT scan for all patients with admission only if an intracranial lesion is present, and (c) skull x-ray for all patients, with admission and head CT only for patients with a skull fracture. They found that Regimen (b) was about 10% less expensive than Regimen (a) because of the reduced number of hospital admissions. They also found that Regimen (c) was about 20–25% less expensive than Regimen (b)—an actual savings of about $50,000 per year for a patient sample of 200 per year—, but they felt that these small savings would likely be reduced by additional expenses related to missed intracranial lesions. They concluded that using the CT as a screening method in these patients not only provides optimal care from a medical standpoint, but is also justified from a cost effectiveness point of view.

Conclusion

Our Recommendations for Emergency Imaging Studies In Patients with Head Trauma

Skull X-ray. There are no clear indications. The skull x-ray may be helpful in cases of gunshot wounds to the head and neck for quick assessment of bullet trajectory.

Head CT. Head CT is indicated for any high-risk criteria; GCS < 15 for any reason, including alcohol; GCS 15 with any moderate-risk criteria (this is controversial).

MRI. There are no clear indications.

Cervical Spine X-ray. This is indicated with GCS < 15; GCS 15 with neck pain or tenderness; any suspicion of a spinal cord injury by history or physical examination

Our Recommendations for Hospital Admission in Patients with Head Trauma

Admission is indicated in a patient with GCS < 15 or GCS 15 with an intracranial abnormality on head CT.

In conclusion, head injury is common, and it is important for the physician caring for patients with head injury to have a plan for evaluating these patients. Most head injuries are in the low-risk category and require no imaging studies. Skull x-rays and CT scans in these patients are costly and not beneficial. For patients with head trauma who are not in the low-risk category, there are several different evaluation regimens that have been suggested. In general, we favor a somewhat more agressive evaluation regimen because it is not only the best form of medical treatment but, by avoiding missed pathology and unnecessary hospital admissions, it is a cost-effective method as well.

References

1. Harders A, Kakarieka A, Braakman R, the German tSAH study group. Traumatic subarachnoid hemorrhage and its treatment with nimodipine. J Neurosurg 1996; 85: 82–89.
2. Stein SC, Young GS, Talucci RC, et al. Delayed brain injury after head trauma: Significance of coagulopathy. Neurosurgery 1992; 30:160–165.
3. Temkin NR, Dikmen S, Wilensky AJ, et al. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med 1990; 323:497–502.
4. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. N Engl J Med 1990; 322:1405–1411.
5. Masters SJ, McClean PM, Arcarese JS, et al. Skull x-ray examinations after head trauma: recommendations by a multidisciplinary panel and validation study. N Engl J Med 1987; 316:84.
6. Orrison WW, Gentry LR, Stimac GK, et al. Blinded comparison of cranial CT and MR in closed head injury evaluation. Am J Neuroradiol 1994; 15:351–356.
7. Sklar EML, Quencer RM, Bowen BC, et al. Magnetic resonance applications in cerebral injury. Radiol Clin North Am 1992; 30:353–366.
8. Balasubramaniam S, Kapadia T, Campbell J, Jackson TL. Efficacy of skull radiography. Am J Surg 1981; 142: 366–369.
9. Masters SJ. Evaluation of head trauma: Efficacy of skull films. Am J Radiol 1980; 135:539–547.
10. Royal College of Radiologists, eds. Costs and benefits of skull radiography for head injury: A national study. Lancet 1981; 2:791–795.
11. Murshid WR. Role of radiography in the initial evaluation of minor head injury: A retrospective study. Acta Neurochir (Wien) 1994; 129:11–14.
12. Feuerman T, Wackym PA, Gade GF, Becker DP. Value of skull radiography, head computed tomographic scanning, and admission for observation in cases of minor head injury. Neurosurgery 1988; 22:449–453.
13. Mohanty SK, Thompson W, Rakower S. Are CT scans for head injury patients always necessary? J Trauma 1991; 31(6):801–805.
14. Harad FT, Kerstein MD. Inadequacy of bedside indicators in identifying significant intracranial injury in trauma patients. J Trauma 1992; 32:359–363.
15. Schynoll W, Overton D, Krome R, et al. A prospective study to identify high-yield criteria associated with acute intracranial computed tomography findings in head-injured patients. Am J Emerg Med 1993; 11:321–326.
16. Stein SC, O'Malley KF, Ross SE. Is routine computed tomography scanning to expensive for mild head injury? Ann Emerg Med 1991; 20(12):1286–1289.

17. Jeret JS, Mandell M, Anziska B, et al. Clinical predictors of abnormality disclosed by computed tomography after mild head trauma. Neurosurgery 1993; 32:9–16.
18. Miller EC, Derlet RW, Kinser D. Minor head trauma: Is computed tomography always necessary? Arch Emerg Med 1996; 27:290–294.
19. Yealy DM, Hogan DE. Imaging after head trauma. Who needs what? Emerg Med Clin North Am 1991; 9(4):707–717.
20. Defensive medicine and medical malpractice: Washington DC: US Congress, Office of Technology Assessment; 1994.
21. Stein SC, Ross SE. The value of computed tomographic scans in patients with low-risk head injuries. Neurosurgery 1990; 26:638–640.
22. Davis RL, Hughes M, Gubler KD, et al. The use of cranial CT scans in the triage of pediatric patients with mild head injury. Pediatrics 1995; 95:345–349.

John E. Moseley, M.D.

1909–1996

The Mount Sinai Hospital throughout its history has been privileged to be associated with many great leaders and pioneers in the field of medicine. In November 1996, one such long-time member of its staff, Dr. John E. Moseley, a distinguished African American radiologist quietly passed away at the age of 87. Dr. Moseley began his association with Mount Sinai in 1944, a relationship that lasted until 1980 when he retired as Emeritus Associate Clinical Professor and Associate Attending Radiologist.

During his lifetime, Dr. Moseley was associated with many firsts. He was a brilliant student. Dr. Moseley's desire to study medicine was kindled at the early age of 12 after a bout of pneumonia. After attending Stuyvesant High School in New York, he matriculated at Harvard College and graduated in 1932. He was awarded the Isham Carpenter Scholarship for excellence in studies and a summer fellowship to the marine biological laboratories in Woods Hole.

He was quite frustrated and angry when his application to Harvard Medical School was rejected despite honor grades and superior recommendations. He was politely informed by the Dean of the Medical School that no black students would be admitted. In fact, none were admitted between the years of 1928 and 1941. John matriculated at the University of Chicago where he again encountered the reality of prejudice confronting black students. The medical school at that time was divided into two separate divisions; Rush Medical School and the Medical School of the Division of Biological Sciences. The latter was located on the campus of the University in South Chicago and affiliated with Billings Hospital.

After successfully completing the first two years and at the beginning of their junior year, students were given the option of going either to Rush or staying on at the Division of Biological Sciences. John elected to go to Rush but was informed that black students had to attend Billings Hospital on the south side. The reason given was that Provident Hospital, which took care only of black patients, had made arrangements with the medical school to train all black students in obstetrics and gynecology. Dr. Moseley thus began a battle with the school. Although the NAACP and the Rosenwald Foundation came to his aid, the University nevertheless prevailed. This experience indelibly imprinted on him the desire for recognition and racial equality.

After graduating from the University of Chicago and completing an internship at Provident Hospital, Dr. Moseley took a few postgraduate courses in gastroenterology at The Mount Sinai Hospital followed by 2 years of training in radiation therapy at Bellevue Hospital under Dr. Ira Kaplan. This was a breakthrough for black physicians in New York City where almost all black physicians were affiliated either with Harlem Hospital or no hospital at all. Needing another year for his Radiology Boards, Dr. Moseley was accepted at The Mount Sinai Hospital by Dr. Marcy Sussman, the Director of the Radiology Department at that time, to complete a third year in diagnostic radiology. As far as I am aware, Dr. Moseley may have been the first African American at Mount Sinai. He was certainly its first pediatric radiologist. This was yet another breakthrough for a black physician. He thus entered an environment replete with other budding giants in radiology at Mount Sinai: Dr. Bernard S. Wolf, who soon became the next Director of Radiology at Mount Sinai, and Dr. Richard S. Marshak, who would become a world-renowned radiologist. What a crew that must have been!

Dr. Moseley completed his training in 1944 and was subsequently certified in diagnostic and therapeutic radiology. He remained at The Mount Sinai Hospital as an Assistant Radiologist in diagnosis and began a career that encompassed 35 years. This period opened many medical pathways for Dr. Moseley and subsequently for many black physicians.

Dr. Moseley soon assumed the Directorship of Radiology at Sydenham Hospital which had a predominantly black patient census and a high incidence of sickle cell disease. He fostered an interest in the bone changes found in this disease. As with all inquisitive minds, one interest leads to another and he was shortly studying other anemias and eventually the bone changes in all hematologic disorders. This culminated in a series of articles to *The Journal of The Mount Sinai Hospital* for which he received the Ralph Colp Award for the best annual contribution to *The Journal.* In 1963, at the request of the publisher Grune & Stratton, those articles were compiled into a text book, "The Radiographic Changes of Hematologic Disorders" (1). This book was well received by the medical community and was considered then, and to this day, to be a classic.

Dr. Moseley throughout his radiologic career remained particularly interested in pediatric radiology and until the late 1960s conducted all the radiographic conferences for radiologists and pediatricians. These were always spectacular events. I joined the Department of Radiology in 1963 and soon became particularly impressed with Dr. Moseley's intellectual depth, his enthusiasm, his love for radiology, and for life in general.

One of Dr. Moseley's greatest talents was an ability to understand a subject and proceed to write an article almost to perfection on the first attempt. A few of his many other contributions consisted of the first descriptions of loculated pneumomediastinum on the chest film (2), the radiologic changes of the lumbar spine in trisomy 21 (3), and the radiologic findings in the skull after shunt therapy for congenital hydrocephalus (4). In addition, Dr. Moseley wrote an outline on the radiographic diagnosis of congenital abnormalities of the small bowel (5) and contributed to many other articles relating to pediatric radiology.

Dr. Moseley's work on bone diseases was recognized throughout the world and he was soon requested by many anthropologists to review x-rays of ancient bones. On one occasion he was invited to Peru for the opening of the Museum of Paleopathology. Here he had the opportunity to review x-rays of Peruvian mummies and ancient skeletal remains. This experience led to his discovery that the porous skulls found so frequently among ancient remains were caused by iron-deficiency anemia. This finding was published in the *American Journal of Radium Therapy and Roentgenology* and he was subsequently invited to lecture on the subject at the National Academy of Science, Washington, DC.

In addition to his many inroads into academic life, Dr. Moseley was involved in many community projects. He became director of the Harlem Cancer Committee spearheading a program of lay education and preaching early cancer diagnosis. He spent much time with the local Sickle Cell Anemia Association and the Manhattan-Central Medical Society in attempts to encourage Harlem physicians to apply for positions at voluntary hospitals throughout the city. He was extremely active in encouraging black college students to study medicine.

Dr. Moseley was an individual who never recognized that barriers existed that couldn't be overcome by work, diligence, and enthusiasm. He was a warm, delightful individual with a great sense of humor! He was truly an inspiration and a role model for all. Mount Sinai can truly be proud of this individual who walked tall.

(I would like to thank Dr. Alan E. Oestreich for providing us with Dr. Moseley's Autobiographical chapter that was included in "A Centennial History of African Americans in Radiology," published in Takoma Park, Maryland, Section on Radiology of the National Medical Association, 1996.)

Jack G. Rabinowitz, M.D.
Mount Sinai School of Medicine

References

1. Moseley JE. Bone changes in hematologic disorders. New York and London: Grune & Stratton; 1963.
2. Moseley JE. Loculated pneumomediastinum in the newborn: Thymic "spinnaker sail" sign. Radiology 1960; 75: 788–790.
3. Rabinowitz JG, Moseley JE. The lateral lumbar spine in Down's syndrome: A new roentgen feature. Radiology 1964; 83:74–79.
4. Moseley JE, Rabinowitz JG, Dziadiw R. Hyperostosis cranii ex vacuo. Radiology 1966; 87:1105–1107.
5. Moseley JE, Rabinowitz JG. Congenital abnormalities of the small bowel. J Mt Sinai Hosp NY 1968; 35:14–51.

Information for Authors

THE MOUNT SINAI JOURNAL OF MEDICINE, established in 1934 as *The Journal of the Mount Sinai Hospital,* is a peer-reviewed general medical journal. It is indexed or abstracted in *Index Medicus, Current Contents, Science Citation Index, Hospital Literature Index, International Nursing Index, Excerpta Medica, Chemical Abstracts, Biological Abstracts,* and major databases. Theoretical and basic science articles for the clinician, reviews, reports of clinical or research experience, articles on any subject affecting the practice of medicine, short notes in any specialty, book reviews, letters, and articles by medical students are welcome. The *Journal* generally follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals as revised in 1997 and modified by *The Journal* to conform to the style employed by it. The *Journal* aims at responding to authors of manuscripts within 8 weeks of submission.

Communications. Manuscripts and correspondence should be addressed to: Editor, *The Mount Sinai Journal of Medicine,* The Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Phone: (212) 241-6108; FAX: (212) 722-6386; e-mail: msjournal@msvax.mssm.edu.

Authorship Responsibility, Financial Disclosure, and Assignment of Copyright. Each author is required to sign (1) the statement on authorship responsibility; (2) the statement on financial disclosure; and (3) either the statement on copyright transfer or (4) the statement indicating that the author is or was a US government federal employee when this work was conducted and prepared for publication. These statements are printed from time to time on a page in the *Journal* entitled "Required Form for Authors" and can be photocopied for use. Copies may also be obtained from *The Journal's* office. Use additional copies of the form if there are more than six authors, and replace with the appropriate number of the author, e.g., 7th, 8th, etc. The signed original form(s) should be submitted with the manuscript.

Manuscript Preparation. Submit manuscripts in triplicate, including three sets of illustrations (see below). **Manuscripts must be typewritten or computer generated, double spaced throughout (including references, legends, and tables),** on one side of 8½ × 11 inch white bond paper with **one inch** margins. Other than the Title Page, the abstract page and each page containing text, legends, or tables should be numbered sequentially in the **top right corner,** and include a heading or header which identifies the last name of the first author in the **top left corner.** Begin a new page for the title page, abstract, initial page of text, references, each table, and legends. A floppy disk, if available, should accompany the manuscript. The label on the disk should specify the name of the first author, the title of the manuscript, how the disk has been formatted, and the word processing system used (DOS, Windows, or Windows 95). PC format is preferred but a high-density formatted Macdisk is acceptable. The text should be in ASCII, Microsoft Word or Wordperfect.

Drugs must be identified by their generic names. Do not use abbreviations on the title or abstract page. Define all abbreviations on first use in the body of the manuscript.

Any material taken directly from other sources must be accompanied by a written statement from both the author and publisher giving permission to *The Journal* for reproducing it. The authors must document in the manuscript that all clinical investigations described in the manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board or its equivalent. The text must indicate that the informed consent of each subject was obtained. If results of experiments on animals are reported in the manuscript, the text must indicate that these studies were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office or its equivalent which supervises such work.

Title Page. The title page must be double spaced, and not numbered. It should indicate (1) title of the article, phrased as concisely as possible; (2) first and last name of each author, middle initials, if any, and not more than two academic degree(s); (3) institutional affiliation and title or rank of each author; (4) name and address of department(s) and institution(s) from which the work originated; (5) the name and address (and voice and FAX telephone numbers if available) of the author who will receive and respond to correspondence; (6) the name and full postal address of the author from whom reprint(s) are to be requested; (7) acknowledgments of sources of grant support; (8) name, place, and date of any conferences at which some or all of the information was presented; and, (9) a running head of fewer than 40 letter spaces. At the bottom of the title page, *list 3 to 10 key words or phrases* to facilitate indexing in accord with Medical Subject Headings from Index Medicus. If more than one sheet is needed, label the supplemental sheet as Title Page ii.

Abstract. All articles must include an abstract on the first numbered page of the manuscript of not more than 250 words. Abstracts should be double spaced and divided into four paragraphs:

Background: what problem(s) was(were) addressed;
Methods: how the study was performed;
Results: the salient results;
Conclusions.

Key Words. Three to 10 key words or phrases must be provided at the bottom of the title page to facilitate indexing. (see above)

Units of Measurement. SI units are preferred, but values may be expressed in conventional units and conversion factors indicated. The range of normal values for the reporting laboratory must be indicated. When conventional units are used in figures or tables, the appropriate conversion factor(s) must be provided in legends or footnotes.

Editing. All papers will be edited to enhance conciseness and clarity without altering meaning and to ensure conformity with journal style. Authors whose primary language is not English should obtain help from someone proficient in English spelling and grammar.

Illustrations. Photographs, line drawings, and graphs should enhance understanding of the text. Three copies of each must be submitted with the manuscript. Line drawings and graphs should be professionally prepared or computer generated and camera ready. Symbols, lettering, and numbers should be large enough to remain easily legible after the figure has been reduced to fit the width of one column. Photographs must be sharp, high contrast, black and white glossy prints not exceeding 5 inches in height × 7 inches in width. The authors must pay attention to the quality of print reproductions of x-ray plates or transparencies to assure that the special features are labeled and will remain easily visible when reduced to fit the width of one column. The name of the subject and hospital number(s) should not be reproduced in the print. Black and white copies of photomicrographs are preferred and must be cropped to a width of 3⅛ inches. The type of stain and power of magnification must be indicated in the relevant legend. Electron photomicrographs should have internal scale markers. On the back of each print and photograph affix a gum label on which the number of the figure has been written to correspond to its identification in the text, title of manuscript, first author's last name, and the word "top" and arrow to indicate the top edge. **Do not write this information directly on the print and do not mount the print on cardboard.** Illustrations which are to appear together should be mounted accordingly as plates and should be equally sized. Protect the prints by enclosing them in cardboard and separate envelopes. **Do not use paper clips.**

Every effort should be made to avoid using a photograph which includes the face or part of the face of a subject. Facial

features should be marked to prevent identification of the subject unless the illustration carries details absolutely essential to the text. **In any case, a partial or full facial photograph of a subject will not be published unless written permission has been obtained from the subject and accompanies the photograph.**

Legends. Legends should not duplicate the text. Each should be on a separate sheet of paper and double spaced. Number each legend to match the illustration it describes. Illustrations mounted as plates to appear together should be accompanied by a single legend identifying the separate elements by position ("upper left," "middle") or by letters. If such illustrations have been labeled with letters, the same letters are to be used in the legend. The legend must indicate the magnification and type of stain used for photomicrographs.

Tables. Each table should be typed on a separate page, double spaced. Number tables consecutively (Table 1, etc.) to correspond to their appearance in the text. Give each table a brief title that is self-explanatory without reference to the text and type the title on a separate line below its number. Identify all abbreviations and/or symbols used in the table in a footnote.

References. All references cited in the text are to be numbered sequentially. Enclose the citation number in parentheses and place it before any punctuation, e.g., **Cytomegalovirus (1), steroids (2,3), and recreational drugs (4–6) have all been implicated (7).** Do not use superscripts. The reference list must be limited to works cited in the text, and numbered in the order in which they are cited. Journal title abbreviations must conform to those used in *Index Medicus*. The styles to be used for various kinds of citations to be listed in the section of the manuscript entitled References are illustrated in the version of "Uniform Requirements" published in the New England Journal of Medicine referenced below. The list of references must be typed, double spaced, on separate pages, following the arrangement and punctuation style as shown in the examples.

1. Brown LK. Sleep apnea syndromes: overview and diagnostic approach. Mt Sinai J Med 1994; 61:99–112.

2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336(4):309–315.

3. Couser WG. Glomerular diseases. In: Stein J. ed. Internal Medicine 2nd ed. Little Brown: Boston, 1987: 834–861.

List the names of all authors when there are four or fewer. When there are five or more, list the names of the first three, then *et al.*

References to unpublished data (unless the information is In press) and personal communications should not be included in the list of numbered references. Instead, such information should be placed in the text in parentheses. Permission must be obtained from the appropriate individual to so quote the material. This permission must accompany the manuscript at the time of its submission. **If the manuscript is accepted for publication, the author(s) will be asked to confirm the accuracy of all references.**

Proofs. Proofs will be sent to the corresponding author as soon as they are available. Stylistic changes should not be made. Because of increased printing charges, the cost of author's alterations beyond routine correction of typographical errors in text and data will be billed to the author. Proofs should be corrected and returned to and received at the editorial office within 48 hours by express delivery at the author's expense to the address listed above ("Communications").

Offprint Orders. An offprint order form will be sent to the corresponding author with the proofs; if offprints are desired, the form must be returned to the editorial office, preferably with the proofs, but not later than 3 days to avoid late charges. A check for the exact amount in US dollars should be made out to the order of *The Mount Sinai Journal of Medicine.* Please indicate on the check the last name of the first author, and the title of the article. If for one reason or another, the offprint order form is not received with the proofs, it may be obtained directly from the editorial office via telephone or FAX. Offprints are available in minimum quantities of 100, at a cost depending on the number of printed pages and whether covers are desired. The cost of other than routine surface mail delivery, if requested, must be added to the cost of the offprints. Information on the cost of other than routine surface delivery can be obtained from the editorial office.

Required Form for Authors:

AUTHORSHIP RESPONSIBILITY, FINANCIAL DISCLOSURE, AND ASSIGNMENT OF COPYRIGHT

Article Title (type):

Each author must read and sign this form dealing with (1) authorship responsibility, (2) financial disclosure and (3) copyright transfer. An author who was a US federal employee when this work was conducted and prepared for publication, must sign statement (4) instead of statement (3).

1. Authorship Responsibility

I certify that I have participated sufficiently in the conception and design of this work, and the analysis of the data (where applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe that the manuscript represents valid work. I have reviewed the final version of the manuscript and approve it for submission for publication. Neither this manuscript nor one with substantially similar content under my (our) authorship has been published or is being considered for publication elsewhere, except as described in a separate attachment. Furthermore, I agree to produce the original recorded data on which the manuscript is based for examination by the Editor-in-Chief and/or his assignees should such records be requested.

2. Financial Disclosure

I certify that I do not have and have not had an affiliation or financial involvement with or in any organization or entity with a direct financial interest in the subject matter or materials being discussed in the manuscript (eg, employment, consultancies, stock ownership, honoraria), except as disclosed in a separate attachment.

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

3. Copyright

In compliance with the Copyright Revision Act of 1976, the signature of each author on this form shall indicate and be evidence of agreement and mutual understanding with *The Mount Sinai Journal of Medicine*, in consideration of the further action of the *Journal* to review and edit the manuscript being submitted, to transfer, assign, and convey all copyright ownership, including any and all rights incidental thereto, exclusively to *The Mount Sinai Journal of Medicine* if this work is published in the *Journal.*

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

4. US Federal Employees

I was an employee of the US federal government when this work was conducted and prepared for publication; therefore, it is not protected by the Copyright Act and copyright ownership cannot be transferred.

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

Return the original signed form to The Editor, The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, N.Y. 10029. Retain one copy of the form for your file. You may make as many photocopies as needed if your manuscript has more than six authors.

LEVY LIBRARY, MT. SINAI MEDICAL CENTER
3 4805 04591885

THE
MOUNT SINAI JOURNAL OF MEDICINE

Forthcoming:

Grand Rounds

Money, Medicine and Methuselah
Christine K. Cassel
The Mount Sinai School of Medicine

Lipostasis and the Control of Body Weight: Cloning of the Obesity (ob) Gene
Jeffrey Friedman
Rockefeller University

The Lactose Permease Meets Frankenstein: New Approaches to Membrane Protein Structure
H. Ronald Kaback
Howard Hughes Medical Institute
University of California, Los Angeles

Silicone Breast Implants and Connective Tissue Disease: An Overview
Harry Spiera and Robert F. Spiera
The Mount Sinai School of Medicine

Theme Issues

Computers in Medicine
Editors: Ray Cornbill and Joseph Kannry

Laparoscopy
Editors: Barry Salky and Michael Edye

Human Immunodeficiency Virus—AIDS
Editor: Henry Sacks

Emergency Medicine
Editors: Andy Jagoda and Lynne Richardson

Reproductive Choice: Genetic Counseling and Assisted Reproductive Technology
Editors: Rosamond Rhodes, Daniel A. Moros, Allyson Robichaud

Available now:

Alumni Theme Issue Part A: Original Articles
Volume 63, Numbers 3&4, 1996
134 pages. $20.00

Cross-Cultural Issues in Psychopharmacology and Alumni Theme Issue Part B
Volume 63, Numbers 5&6, 1996
154 pages. $20.00

THE
MOUNT SINAI JOURNAL
OF MEDICINE

VOLUME 64 NUMBERS 4 & 5 SEPTEMBER/OCTOBER 1997

SEP -5 1997

EMERGENCY MEDICINE

Guest Editors: Andy Jagoda and Lynne Richardson

Veterans
Affairs

THE MOUNT SINAI JOURNAL OF MEDICINE

The Mount Sinai Journal of Medicine is published by The Mount Sinai Medical Center of New York and has the following affiliates: Bronx Veterans Affairs Medical Center, New York; Elmhurst Hospital Center, Queens, NY; Queens Hospital Center, Queens, NY.

Editor-in-Chief

Sherman Kupfer, M.D.

Editor Emeritus

Lester R. Tuchman, M.D.

Associate Editors

Harriet S. Gilbert, M.D. Julius Wolf, M.D.

Administrative Assistant

Joseline Ilagan

Assistant Editor for Housestaff

Rochelle Waldman, M.D.

Michael E. Blam, M.D.

Assistant Production Assistant

Mel Meyer

Assistant Editors

David H. Bechhofer, Ph.D.
Constanin A. Bona, M.D., Ph.D.
Edward J. Bottone, Ph.D.
Lewis Burrows, M.D.
Christopher P. Cardozo, M.D.
Mark R. Chassin, M.D., MPH, MPP
Joseph S. Eisenman, Ph.D.
Richard A. Frieden, M.D.
Frederick Friedman, M.D.
Steven Fruchtman, M.D.
Paul L. Gilbert, M.D.
James N. Gladstone, M.D.
James H. Godbold, Ph.D.
Richard S. Haber, M.D.
Noam Harpaz, M.D.
Tomas Heimann, M.D.
Sheldon Jacobson, M.D.
Barry W. Jaffin, M.D.
Joseph L. Kannry, M.D.
Suzanne Carter Kramer, M.Sc.
Mark G. Lebwohl, M.D.
Zvi Lefkowitz, M.D.
Kenneth V. Lieberman, M.D.
Lynda R. Mandell, M.D., Ph.D.
Steven Markowitz, M.D.
Bernard Mehl, D.P.S.
Myron Miller, M.D.
Edward Raab, M.D.
Elliot J. Rayfield, M.D.
Allan Reed, M.D.
Clive Rosendorff, M.D., Ph.D.
Fred Rosner, M.D.
Allan E. Rubenstein, M.D.
David B. Sachar, M.D.
Henry Sacks, M.D.
Ira Sanders, M.D.
Martin H. Savitz, M.D.
Clyde B. Schechter, M.D.
Stuart C. Sealfon, M.D.
Michael Serby, M.D.
Phyllis Shaw, Ph.D.
Alex Stagnaro-Green, M.D.
Barry D. Stimmel, M.D.
Nelson Stone, M.D.
Max Sung, M.D.
Rein Tideiksaar, Ph.D.
Richard P. Wedeen, M.D.
Vincent B. Ziccardi, M.D., D.D.S.

Editorial Board

Barry S. Coller, M.D.
Barry Freedman, M.B.A.
Richard Gorlin, M.D.
Nathan Kase, M.D.
Panayotis G. Katsoyannis, Ph.D.
Charles K. McSherry, M.D.
Jack G. Rabinowitz, M.D.
John W. Rowe, M.D.
Alan L. Schiller, M.D.
Alvin S. Teirstein, M.D.
Rosalyn S. Yalow, Ph.D.

The Mount Sinai Journal of Medicine (ISSN No. 0027-2507; USPS 284-860) is published 6 times a year in January, March, May, September, October, and November in one indexed volume by The Mount Sinai Medical Center, Box 1094, One East 100th Street, New York, NY 10029-6574. Subscription price: individuals (U.S. and Canada), $75 per year; libraries and institutions (U.S. and Canada), $115 per year; individuals (outside U.S. and Canada), $100 per year; libraries and institutions (outside U.S. and Canada), $140 per year. Single copies $20. New subscriptions begin with the first issue of the calendar year. Send notice of change of address 60 days before its effective date. Periodicals postage paid at New York, NY and at additional mailing offices. POSTMASTER: Send address changes to The Mount Sinai Journal of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Telephone number (212) 241-6108; Fax (212) 722-6386. Copyright 1997 The Mount Sinai Hospital.

DISCLAIMER: The statement and opinions expressed in the *Journal* by authors and contributors are solely their own and not those of The Mount Sinai Medical Center or The Mount Sinai Journal of Medicine. All advertisements are expected to conform to ethical standards, and their appearance does not imply endorsement or approval by The Mount Sinai Medical Center and/or The Mount Sinai Journal of Medicine of the products with respect to effectiveness, quality, or safety. The Mount Sinai Medical Center and The Mount Sinai Journal of Medicine do not hold themselves responsible for statements made by the authors or contributors, and for any injury to persons or property which may have resulted from ideas, products, and services referred to in articles or advertisements.

COPYRIGHT: Material printed in the Journal is protected by copyright. In accord with U.S. Copyright law, no part of the Journal may be reproduced, displayed, or transmitted in any form, electronic or mechanical, including photocopying or by any information storage or retrieval system, without prior written permission to do so. Permission should be requested from The Editor. The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574.

THE
MOUNT SINAI JOURNAL
OF MEDICINE

Volume 64
Numbers 4 & 5
September/October 1997

CONTENTS

ANNOUNCEMENT OF 1996 AWARDS iii

PART A

Introduction: Issues in Emergency Care and Resuscitation
Sheldon Jacobson 239

Acute Stroke: Emergency Management and Future Interventions
Denise Nassisi 241

The Evaluation and Treatment of Seizures in the Emergency Department *Andy Jagoda and Lynne Richardson* 249

Emergency Department Management of Acute Myocardial Infarction *Edward Mintz* 258

Management of Life-Threatening Asthma in the Emergency Department *Lynne Richardson and Andy Jagoda* 275

Poisoning and Overdose *Diane F. Giorgi and Andy Jagoda* 283

Emergency Airway Management *Paul H. Hamilton and*
John J. Kang 292

Pediatric Trauma *Matthew J. Kapklein and Robby Mahadeo* 302

The Evaluation of Blunt Abdominal Trauma: The Evolving Role of Ultrasound *Sheree Givre and Stuart Kessler* 311

Vascular Emergencies *Denise C. Semashko* 316

Disaster Medicine *Neill S. Oster* 323

Severe Head Injury: Prehospital and Emergency Department Management *Salvatore Silvestri and Susan Aronson* 329

PART B

Nontraumatic Intramural Hematoma of the Duodenum Complicating Warfarin Therapy *David E. Gutstein and*
Stanley J. Rosenberg 339

Splenic and Renal Infarctions Complicating Atrial Fibrillation
Athanassios Argiris 342

continued

THE
MOUNT SINAI JOURNAL
OF MEDICINE

Volume 64
Numbers 4/5
September/October 1997

CONTENTS *continued*

The Stuck Catheter: A Case Study *Philip K. Ng, Mark J. Ault, and Michael C. Fishbein* 350

DERMATOLOGY NOTES

Acute Meningococcemia *Allen Sapadin, Marsha Gordon, and Edward J. Bottone* 353

OPHTHALMOLOGY NOTES

Angle-Closure Glaucoma *Arif Khan* 354

BOOK REVIEWS

Our Health, Our Lives: A Revolutionary Approach to Total Health Care for Women *Harriet S. Gilbert* 355

Keep on Running: The Science of Training and Performance *Sherman Kupfer* 356

Abdominal Access in Open and Laparoscopic Surgery *A. James McElhinney* 356

Crohn's Disease *Lawrence S. Friedman* 357

Information for Authors 359

Required Form for Authors 361

Correction

We regret that an error was made in the printing of the name of the guest editor on the cover of the previous issue, Volume 64, Issue 3, May 1997. The correct name of the guest editor is Martin H. Savitz. A special self-adhesive label on which Dr. Savitz's full name has been printed correctly is available and has been included in this mailing package sent to all subscribers. The label can be positioned over the incorrect printing on the cover of issue 3. If for some reason the label has been lost or misplaced, and you wish to use such a label, please request one by writing directly to *The Mount Sinai Journal of Medicine,* Box 1094, One East 100th Street, New York, NY 10029. Please indicate your full name and address on the request.

Announcement of 1996 Awards

The Mount Sinai Journal of Medicine offers several prizes for manuscripts published in *The Journal* during the previous year and judged by an independent Awards Committee to be outstanding contributions to the medical literature. The committee's task certainly was formidable, but as expected, I believe that it has chosen wisely and well. The efforts of the members are much appreciated.

The 1996 Ralph Colp Award honors the memory of a distinguished Chief of Surgery at The Mount Sinai Hospital. It is for the best paper on a surgical topic. The award goes to Dr. Evelyn R. Barrack, Associate Professor of Urology at The Johns Hopkins University School of Medicine, for her paper entitled, "Androgen Receptor Mutations in Prostate Cancer," which appeared in Volume 63, Nos. 5 & 6, pp. 403–412.

The 1996 Joseph Globus Award, established in honor of the first and long-time editor of *The Journal,* is for the best overall paper on a clinical topic. The chairperson of the Awards Committee informed me, after a prolonged discussion and many secret ballots by the members of the committee, that they were unable to select a single paper from the many which had been nominated. Therefore, the committee recommended that two papers be designated as recipients of the 1996 Globus Award. I am presenting them in chronologic order of their publication. The first award goes to Drs. Lloyd Mayer, Xian Yang Yio, Ms. Annica Lin, and Dr. Asit Panja for their manuscript entitled, "Pathogenesis of Inflammatory Bowel Disease: Evolving Concepts," which appeared in Volume 63, Nos. 3 & 4, pp. 202–209. Dr. Mayer is Professor of Medicine at the Mount Sinai School of Medicine, and his co-authors are his colleagues in the Division of Clinical Immunology of the Department of Medicine. The second award goes to Drs. Ronald S. Freudenberger and Valentin Fuster for their manuscript entitled "Fifty Years of Experience with Antithrombotic Therapy in Cardiac Disease: A 1996 Approach Based on Pathogenesis and Risk," which appeared in Volume 63, Nos. 5 & 6, pp. 342–358. Dr. Freudenberger is now a member of the faculty of the University of Maryland, serving as Director of Cardiac Transplantation. Dr. Fuster is Dean for Academic Affairs, Director of the Cardiovascular Institute, and Professor of Medicine of the Mount Sinai School of Medicine.

On behalf of The Editorial Staff, I am delighted to recognize the outstanding scholarship and contributions of our 1996 Awardees to medicine in general, and to *The Mount Sinai Journal of Medicine* in particular.

Sherman Kupfer, M.D.
Professor of Medicine
Physiology and Biophysics
Editor-in-Chief

Introduction

SHELDON JACOBSON, M.D.
FACEP, Professor and Chair
Department of Emergency Medicine
Mount Sinai School of Medicine
New York

Issues in Emergency Medical Care and Resuscitation

EMERGENCY MEDICINE is a young specialty which gained recognition in 1989 as the twenty-third medical specialty with an independent board. There are now approximately 114 emergency medicine residencies and more than 40 academic chairs of emergency medicine in American medical schools. There are approximately 1300 residents graduating from accredited emergency medicine programs each year. In 1995, there were 14,250 physicians certified by the American Board of Emergency Medicine. The Society for Academic Emergency Medicine's Manpower Task Force estimates that there is a need for 40,000 emergency medicine specialists.

As an established clinical discipline, Emergency Medicine has taken its rightful place of leadership in the initial diagnosis and management of acutely ill or traumatized patients. Various studies have shown that approximately 50% of emergency department patients have critical or urgent conditions which require immediate attention (1). The remainder have less acute illnesses, exacerbations of chronic diseases, or a minor illness which they perceive as an emergency, or they are seeking care in the emergency department for reasons of convenience or lack of primary health care resources. Most emergency physicians welcome these patients into their departments and seek to provide them with high-quality expeditious care while referring them to a primary heath care provider or network. Interest in the variety of patients who use the emergency department has led to the development of subspecialties in emergency medicine such as prehospital care, toxicology, pediatric emergency medicine, sports medicine, and occupational medicine. Special interest focus groups have developed in areas such as pain management, injury prevention, asthma care, and international medicine.

The research interests of emergency physicians initially centered on clinical management issues. There was a focus on entities which have serious prognoses such as cardiopulmonary arrest, multisystem trauma, and poisoning and overdose. More recently, emergency physicians have extended their research efforts into the basic sciences and are actively involved in contributing to the understanding of the pathophysiology of many disease and injury processes including stroke, myocardial infarction, and shock. Emergency physicians and their colleagues in other disciplines have worked arduously to promulgate management guidelines for critically ill patients. The American College of Emergency Physicians has worked with other specialties in the development of practice guidelines in several areas including the management of severe brain injury, myocardial infarction, seizures, and asthma. Efforts initiated by the American Heart Association and embraced by emergency physicians have led to the periodic review of cardiac care standards and to the training of thousands of providers in Advanced Cardiac Life Support according to American Heart Association standards.

The foundation of modern resuscitation is based on the establishment and maintenance of the patient's airway, breathing, and circulation. This foundation was initiated by the seminal contributions of Kouwenhoven, Knickerbocker, and Jude who rediscovered closed chest compression, building on the initial observations made in the literature by Crile in 1904 (2). Mouth-to-mouth ventilation was investigated by Safar who demonstrated that this technique could maintain near-normal oxygenation in experimental subjects

(3). All four of these investigators collaborated in the uniting of mouth-to-mouth ventilation with closed chest compression. Thus basic life support, cardiopulmonary resuscitation, was launched and a revolution began in resuscitation. The recognition of cardiac sudden death and its relationship to ventricular fibrillation ultimately led to the development of the defibrillator. Original work by Kouwenhoven in animals was followed by the development of the alternating current internal defibrillator by Beck, who is credited with the first successful internal defibrillation in 1947 (4). The alternating current external defibrillator was perfected by Zoll in 1956 (5), and the subsequent replacement of alternating shock with direct current pulses by Lown (6) created a revolutionary capability for effectively managing cardiac arrest. These advances were elegant, yet simple, in both theory and practice, and were promptly exported from the hospital to the prehospital setting (7). In the 1980s Mirowsky designed and implanted the first automated internal defibrillator in patients with recurrent malignant ventricular rhythm disturbances (8). In the late 1980s several biomedical companies and clinical investigators designed and successfully tested the first of a series of automated external defibrillators which, through voice simulation and computer recognition, guide rescuers with minimal training through the safe administration of defibrillating shocks to cardiac arrest victims (9).

The explosive developments in resuscitation during the past 30 years made the greatest advances in the area of stabilization. However, outcome studies have clearly demonstrated that the establishment of cardiopulmonary function alone is not sufficient to ensure a successful clinical recovery. Successful resuscitations depend on the timely initiation of care and on the prevention of injury at the cellular level, two areas that are intimately related. This is best demonstrated by a recent epidemiological study from New York City which revealed that the survival from cardiac arrest, defined as patients discharged alive from hospital, was only 5.3% versus rates that are more than double in other cities (10). This disturbing finding is caused in part by delays in the initiation of care. Consequently, at the present time, two of the major areas of research in emergency medical care and resuscitation are in emergency medical service systems and in finding ways to protect and salvage cells subjected to ischemic injury.

This issue of *The Mount Sinai Journal of Medicine* is dedicated to providing a perspective on some of the advances and challenges in emergency medical care. Recognizing potentially unstable patients, ensuring proper stabilization, and instituting timely care, the three key components in emergency medicine, are recurrent themes throughout this issue of *The Journal*. Recognition of potentially unstable patients is made particularly evident in the sections on poisonings, seizures, asthma, vascular emergencies, and disaster medicine. Ensuring proper stabilization is the focus of the sections on pediatric trauma, abdominal trauma, brain injury, and airway interventions. Tissue preservation from the overwhelming insults of ischemic and reperfusion injury have posed hard-to-overcome barriers to successful resuscitation but appear to be ultimately amenable to pharmacological manipulation: The importance of the institution of timely care is presented in the sections on myocardial infarction, central nervous system resuscitation, and brain injury. Hopefully, the topics reviewed in this issue will promote thought and discussion and identify areas needing research.

References

1. Gill J. Nonurgent use of the emergency department: Appropriate or not? Ann Emerg Med 1994; 24:953–957.
2. Kouwenhoven W, Jude J, Knickerbocker G. Closed chest cardiac message. JAMA 1960; 173:94–97.
3. Safar P. Ventilatory efficiency of mouth-to-mouth artificial respiration. JAMA 1958; May:335–341.
4. Becker C, Pritchard W, Feil H. Ventricular fibrillation of long duration abolished by electrical shock. JAMA 1947; 135:985–986.
5. Zoll P, Lurenud A, Gibson W. Termination of ventricular fibrillation in man by internally applied electric countershock. N Engl J Med 1956; 254:727–732.
6. Lown B, Amarasingham R, Neumon J. New method for terminating cardiac arrhythmias: Use of synchronized capacitor discharge. JAMA 1962; 182:548–555.
7. Pantridge J, Gedder S. A mobile intensive care unit in the management of myocardial infarction. Lancet 1967; II: 271–273.
8. Mirowski M, Mower M, Staewen W. Standby automatic defibrillation. Arch Intern Med 1970; 126:158–161.
9. Weaver W, Hill D, Fahrenbruch C. Use of the automatic external defibrillator in the management of out-of-hospital cardiac arrest. N Engl J Med 1988; 319:661–666.
10. Lombardi G, Gallagher J, Gennis P. Outcome of out-of-hospital cardiac arrest in New York City. JAMA 1994; 271:678–683.
11. Kannel W. Meaning of the downward trend in cardiovascular mortality. JAMA 1982; 247:877–880.

Acute Stroke

Emergency Management and Future Interventions

Denise Nassisi, M.D.

Abstract

Stroke is a major cause of death and disability. Early intervention in the emergency department has become increasingly important in improving stroke outcome as effective therapies are used. Current emergency evaluation and management of ischemic (thromboembolic) stroke, intracerebral hemorrhage, cerebellar stroke, subarachnoid hemorrhage, and transient ischemic attacks is discussed. Recent developments in stroke therapeutics including thrombolytics, low-molecular-weight heparins, excitatory amino acid antagonists, free radical scavengers, gangliosides, and leukocyte inhibitors are reviewed.
Key Words: stroke, thrombolytics, transient ischemic attacks, subarachnoid hemorrhage.

Several promising approaches to the treatment of stroke have prompted a new urgency in the evaluation and treatment of patients with stroke. Early recognition and prompt initiation of treatment can improve the clinical outcome. Consequently, an educational campaign is underway to increase awareness of stroke symptoms and of the need to view these "brain attack" symptoms with the same sense of urgency as chest pain or "heart attack." Increased public awareness, changes in emergency medical services guidelines, emergency department triage criteria, and the development of hospital stroke teams are helping to expedite the treatment of stroke victims.

Stroke is the third leading cause of death in the United States (1). There are 500,000 new strokes per year (1). Of patients with ischemic stroke, 15 to 30% die within 30 days (2). The mortality of hemorrhagic stroke is even higher, with 40 to 84% dying within 30 days (2). Stroke is the leading cause of disability (1), and the estimated annual cost of stroke is approximately $30 billion per year (3). These imposing statistics manifest the need for more effective stroke management strategies.

Strokes are broadly classified into several categories which elucidate etiology and guide specific management. More than 80 to 85% of strokes are ischemic (thromboembolic), 10 to 15% are intracerebral hemorrhages, and 6 to 7% are subarachnoid hemorrhages (4). The spectrum of the clinical presentations of stroke is broad and ranges from isolated motor or sensory deficits to coma. Several classical stroke syndromes are well recognized and correspond to the anatomic region of the brain which is affected (see Table 1). Although the initial management of stroke does not depend on identifying the exact anatomic distribution of the stroke, it is necessary to determine quickly into which broad type it falls in order to guide emergency management. The physician must be able to distinguish between ischemic stroke, intracerebral bleed, subarachnoid hemorrhage, cerebellar stroke, and transient ischemic attack.

General Emergency Management

The initial role of the emergency department in treating a patient with a suspected intracranial event is the prompt stabilization and evaluation of the patient. There must be a rapid assess-

---

From the Department of Emergency Medicine, Mount Sinai School of Medicine, New York. Address correspondence to Denise Nassisi, M.D., Box 1149, Mount Sinai School of Medicine, Department of Emergency Medicine, New York, NY 10029.

TABLE 1
Stroke Syndromes

- **Dominant (left) hemisphere**
  - Contralateral weakness, numbness, and visual field cut
  - Dysarthria
  - Aphasia
- **Nondominant (right) hemisphere**
  - Contralateral weakness, numbness, and visual field cut
  - Contralateral neglect
  - Constructional apraxia
  - Dysarthria but not aphasia
- **Vertebrobasilar**
  - Dizziness, vertigo, diplopia, dysphagia, ataxia, cranial nerve palsies, bilateral limb weakness
  - Crossed defects (ipsilateral cranial nerve defects with contralateral motor weakness)
- **Basilar**
  - Quadriplegia, coma, locked-in syndrome
- **Middle cerebral artery**
  - Contralateral sensory and motor deficit with arm and face weaker than leg
  - May have aphasia if dominant hemisphere involved
- **Anterior cerebral artery**
  - Leg weakness greater than arm weakness
  - Mild contralateral cortical sensory deficit
  - Dyspraxia
- **Pure motor**
  - One-sided weakness of face and limbs
- **Pure sensory**
  - One-sided decreased sensation of face and limbs

ment of the patient's airway, breathing, and circulatory status. The vital signs of the patient who has had a stroke require close monitoring, especially blood pressure. The data defining optimum blood pressure levels in the patient who has had a stroke are insufficient, however. Although there is concern about the detrimental effect of higher blood pressure, there is also concern that rapid lowering of elevated blood pressure can cause deterioration because of the stroke-induced loss of cerebral autoregulatory mechanisms. Guidelines have been established by the National Stroke Association which were determined by committee consensus (5). It is generally recommended that the blood pressure not be treated urgently unless the systolic pressure exceeds 220 mm Hg or the diastolic pressure exceeds 120 mm Hg on three repeated measurements made at 15-minute intervals. Further, cardiac monitoring and an electrocardiogram (ECG) must be performed because of the coincidence of dysrhythmias and myocardial ischemia with stroke. If fever is present it should be promptly reduced with antipyretics because experimental evidence suggests that lowering temperature reduces the size of infarct (6). The presence of fever warrants the search for a cause and consideration of an infectious etiology of the neurologic deficit.

Determination of serum glucose is important. Hypoglycemia may mimic stroke by producing focal neurologic findings, and it must be corrected promptly by the administration of glucose. However, administration of excess glucose in patients with stroke should be avoided. Some studies have correlated poor stroke outcome with elevated blood glucose (6), but a causal relationship has not been established.

Stroke intervention depends on what type of stroke is involved, and the emergency physician must attempt to delineate this. Another important objective of the emergency department's work-up is to uncover nonstroke conditions that produce a stroke-like presentation (see Table 2). A thorough history, general physical examination, and neurologic examination are required. Focal neurologic deficits should be carefully documented so that any change can be recognized. The presence of possible co-morbidities, which may have caused or contributed to the stroke, including carotid bruits, heart murmurs, and dysrhythmias should be noted. Initial evaluation should include an ECG, chest x-ray, complete blood count, coagulation profile, serum electrolytes, and glucose. An emergency computed tomogram (CT) of the head must be performed, and early neurologic consultation is recommended.

Although seizures are a potential complication of acute stroke during the first 24 hours, routine prophylaxis is not recommended (6). When seizures do occur they are managed initially with lorazepam with consideration given to phenytoin loading. Elevated intracranial pressure is a serious complication of stroke, and patients with neurologic compromise secondary to increasing intracranial pressure are candidates for intubation and hyperventilation. Stabilization using mannitol osmotic therapy is best guided by monitoring intracranial pressure. Immediate neurosurgical consultation must be obtained in all cases of suspected elevated intracranial pressure.

Ischemic Stroke

Ischemic strokes (thromboembolic strokes) are the most common type of stroke. They result

TABLE 2
Conditions That Can Mimic Stroke

- Space-occupying lesions (tumor, epidural or subdural hematoma, abscess)
- Complicated migraine
- Encephalitis/meningoencephalitis
- Metabolic abnormalities (hypoglycemia, hyponatremia, hypernatremia, hyperosmolality)
- Postictal (Todd's) paralysis
- Peripheral neuropathy
- Labyrinthitis

from an area of focal ischemia caused by occlusion of a cerebral vessel by thrombus or embolism. The severity of the decrease in blood flow depends on the size of the involved vessel and the availability of collaterals. The dense ischemic core is surrounded by a marginally perfused ischemic penumbra. The ischemia leads to acidosis with resulting cytotoxic edema caused by intracellular accumulation of sodium, chloride, and water. Eventually microvascular damage leads to breakdown of the blood-brain barrier and results in vasogenic edema. In experimental models it has been shown that after occlusion of a vessel this ischemic zone can be salvaged with reperfusion. The timing of reperfusion is critical; its success is limited to only a few hours. Later reperfusion can actually be harmful and cause formation of additional edema (4).

Thrombolytic Therapy for Ischemic Stroke

Early studies using thrombolytic therapy reported poor outcomes. However, these studies were undertaken before the availability and use of head CTs. The success of thrombolytic therapy in the treatment of acute myocardial infarction spurred new interest in its use for brain infarcts, but unfortunately there are several characteristics that are unique to stroke that make the use of thrombolytic therapy more complex than its use in myocardial infarctions (see Table 3).

Thrombolytic therapy can be given as a selective intra-arterial injection or as a systemic intravenous infusion. Because intra-arterial thrombolytic therapy offers the advantage of direct treatment, it has less systemic complications, but local complications persist. Numerous small open studies have been published, but the results are inconclusive because of the small number of patients and unblinded study design (7, 8). There appears to be some benefit to intra-arterial infusions, but they are generally not used for several reasons: the risk of hemorrhagic transformation of the stroke persists, the therapy is technically difficult and requires a skilled invasive neuroradiologist, and it is not readily available at all centers at all times.

TABLE 3
Factors Complicating the Use of Thrombolytics in Stroke

1. Patients tend to present several hours after onset of symptoms.
2. A head CT must be performed to rule out hemorrhage or other lesion, and the scan must be interpreted quickly and correctly.
3. There is a possibility of a hemorrhagic transformation with or without therapy, and it is not entirely clear who is at risk for this transformation.
4. The measurement of an endpoint to evaluate efficacy is difficult with the use of complex neurologic and disability scoring scales to measure brain function.

Intravenous thrombolytic therapy has the advantage of ease of administration with no requirement of skilled interventional personnel. This therapy still requires that a CT scan be obtained promptly and interpreted correctly before initiation of treatment. Several multicenter, randomized, double-blind trials of intravenous thrombolytic therapy have recently been completed. The European Cooperative Acute Stroke Study (9) evaluated the efficacy of tissue plasminogen activator (TPA) versus placebo in patients with ischemic stroke up to 6 hours from onset. The study demonstrated some improvements in functional and neurologic measures in the TPA treatment group, but these did not outweigh the higher mortality in that group at 30 and 90 days. There was a statistically significant number of protocol violations in the patients randomly selected for the TPA group, however, including misreadings of the initial CT scan, which may have accounted for the increased proportion of bleeding and death in the TPA treatment group.

The Multicenter Acute Stroke Trial-Italy Group (10) evaluated the efficacy of streptokinase with aspirin, streptokinase alone, and aspirin alone versus placebo and enrolled patients up to 6 hours from onset of an ischemic stroke. The streptokinase group had a higher 10-day case fatality rate. Aspirin and streptokinase seemed to reduce 6-month fatality and disability, but the improvement was not statistically significant. The Multicenter Acute Stroke Trial-Europe Study Group evaluated streptokinase in the treatment of middle cerebral artery infarcts within 6 hours (11). This trial was halted because of the high frequency of hemorrhagic transformation and increased mortality in the treatment group. At 6 months streptokinase-treated survivors did have greater functional improvement, but it is unclear if the treatment truly improved function or if those more severely afflicted died early because of complications. Overall, the patients in this study had poor prognosis and high mortality as evidenced by the placebo group. It has been postulated that hemorrhagic transformations induced by thrombolytic therapy may occur more frequently in “severe” strokes, and patients with milder strokes may have a different response. The Australian Streptokinase Trial also enrolled patients up to 6 hours and measured an increase in mortality in the streptokinase-treated group (12).

The National Institute of Neurologic Disorders and Stroke TPA Stroke Study Group used TPA and enrolled patients within 3 hours of the onset of ischemic stroke (13). There was no significant difference in mortality between the TPA and placebo groups. The TPA-treated patients were 30% more likely to have minimal or no disability at 3 months by each of the four outcome measures used. TPA resulted in a more favorable outcome regardless of the subtype of stroke (small vessel thrombus, large vessel thrombus, or cardioembolic). This study demonstrated a clear benefit for TPA treatment within 3 hours of the onset of ischemic stroke. It appears that thrombolytic therapy will not be a panacea for all patients with stroke, but there is a probable benefit for subgroups of patients. A meta-analysis of the data from all five of these trials is being conducted to identify these subgroups and plan future trials (11).

Anticoagulation for Ischemic Stroke

The first studies of heparin use in ischemic stroke were conducted before the advent of CT scans. These very early studies suggested some benefit of heparin and led to its increased use. More recent studies have failed to substantiate the benefit of heparin in acute ischemic stroke. A randomized trial in 1986 failed to demonstrate any benefit, but patients were enrolled up to 48 hours after the onset of symptoms (14). A 1988 trial of heparin failed to prevent progressing ischemic infarction (15).

In cardioembolic stroke, anticoagulation is thought to prevent recurrences and this has been substantiated by several studies (16, 17). What remains controversial in embolic stroke is the timing of anticoagulation. Patients with embolic stroke are at risk for hemorrhagic transformation, and therefore, anticoagulation could cause deterioration. There has been a trend to delay heparin therapy in embolic strokes that have severe symptoms and manifest large infarcts on CT, because these factors are considered to increase the risk of hemorrhagic transformation. A recent study by Chamorro and colleagues (18) suggests that this cautious delay may be unnecessary. This study did find an increased rate of hemorrhagic transformation, but in patients whose partial thromboplastin time was greater than two times control. It indicates the need for careful control of anticoagulation.

Low-molecular-weight heparin may be at least as effective and easier to regulate than standard unfractionated heparin with decreased bleeding complications. It offers ease of administration with once or twice daily subcutaneous injections, increased reliability of anticoagulant effect with predictable bioavailability, fixed dosing based upon body weight, and a decreased incidence of thrombocytopenia (19). It may be that patients with stroke who do not require a continuous intravenous infusion receive earlier mobilization and physical therapy, which possibly results in a decreased length of hospital stay. A recent study of the low-molecular-weight heparin, nadroparin calcium, enrolled patients within 48 hours of ischemic stroke and demonstrated improved outcome at 6 months with no significant increase in the rate of hemorrhagic transformation (20). Currently, the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) is ongoing. TOAST is a multicenter, randomized, double-blind, placebo-controlled study investigating the safety and efficacy of this low-molecular-weight heparinoid for treatment of acute nonhemorrhagic stroke initiated within 24 hours (21).

Antiplatelet Agents for Ischemic Stroke

It was anticipated that antiplatelet agents would be of benefit in acute stroke in the same way that aspirin had a significant benefit in acute myocardial infarction. Antiplatelet agents have been proven beneficial in the prevention of stroke after transient ischemic attack and in the prevention of recurrent stroke (22). However, antiplatelet agents have not yet been shown to be efficacious in the acute treatment of stroke.

Surgical Intervention for Ischemic Stroke

Immediate surgical intervention has also been considered for acute stroke. Emergency middle cerebral embolectomy may benefit selected patients (23), and carotid endarterectomy has proven efficacy in the prevention of stroke in symptomatic patients with high-grade carotid stenosis (24). Whether emergency carotid endarterectomy will be of value in the treatment of stroke remains unknown. In one small series, Meyer and colleagues (25) reported that patients with known carotid stenosis who developed their stroke symptoms while in the hospital, and underwent rapid carotid surgery, had an improved outcome.

Intracerebral Hemorrhage

Intracerebral hemorrhages account for 10 to 15% of all strokes and have a poorer prognosis and a higher mortality rate than cerebral infarctions. Intracerebral hemorrhage may be clinically indistinguishable from cerebral infarction, hence the importance of CT scan evaluation. Patients with intracerebral hemorrhages are more likely to have headache, lethargy, nausea, and vomiting. These patients tend to comprise younger population, and they generally present with marked hypertension. Patients with intracerebral hemorrhage are more likely to rapidly deteriorate with an increased need for intubation.

Most intracerebral hemorrhages are associated with chronic hypertension. Bleeding occurs directly into the brain parenchyma; this is thought to be caused by blood leakage from small intracerebral arteries damaged by chronic hypertension. Other causes include bleeding diathesis from iatrogenic anticoagulation, amyloidosis, and cocaine abuse. A small area of brain is probably irreversibly damaged by the hemorrhage. However, surrounding the hemorrhage there is likely to be an area of reversible damage. The surrounding tissue is damaged by increased pressure and local vasospasm caused by the release of vasoactive substances. It is believed that damage can be reduced by clot removal to reduce pressure and pharmacologic measures to counteract the vasoactive toxic substances released. At present, surgical evacuation of the hematoma remains controversial. Emergency evacuation is used frequently in Japan (26, 27). Previous studies have not shown a benefit, but more recent studies have demonstrated an improvement if surgical evacuation is performed early in the course (28). Ventriculostomy is appropriate urgent management for associated acute hydrocephalus. Early neurosurgical consultation is mandatory for all patients with intracerebral hemorrhage.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage classically presents as the sudden onset of a severe headache (the worst headache of one's life). The headache is often occipital or nuchal. It is often associated with vomiting and a decreased level of consciousness or may present with syncope or seizures. It may present with focal neurologic deficits secondary to the aneurysm or blood compressing adjacent brain or cranial nerves. The Hunt and Hess classification is a clinical grading system for subarachnoid hemorrhage (29) (see Table 4). Subarachnoid hemorrhages occur in a younger patient population and account for half of all strokes in patients younger than 45 years of age. They are associated with a very high mortality accounting for 10% of all deaths from stroke (4). The diagnosis of subarachnoid hemorrhage can be made by CT scan in up to 95% of cases (5). However, in suspected subarachnoid bleed, a "normal" CT is not definitive, and a lumbar puncture is required.

TABLE 4
Hunt and Hess Clinical Grades of Subarachnoid Hemorrhage[a]

Grade	Symptoms
1	Asymptomatic or minimal headache or stiff neck
2	More severe headache, stiff neck
3	Drowsy or confused, may have mild hemiparesis
4	Deeply stuporous, may have moderate to severe hemiparesis, early decerebrate signs
5	Deeply comatose, decerebrate rigidity

[a] See reference 29.

Subarachnoid hemorrhage results when a blood vessel ruptures directly into the subarachnoid space. Most are caused by berry (saccular) aneurysms most often located in the anterior portion of the Circle of Willis. A smaller number are caused by arteriovenous malformations. There is an immediate increase in intracranial pressure which can result in irreversible brain damage. In those who survive the initial hemorrhage, management focuses on the prevention of rebleeding and on the treatment or prevention of vasospasm and hydrocephalus which may cause further morbidity and mortality. The risk of rebleeding is greatest in the first 48 hours and is associated with a high mortality rate. Surgical clipping of the involved aneurysm is of proven benefit, although the timing of surgery remains under debate. The Hunt and Hess System is used to assist decision making. Patients with Hunt and Hess Grades 1 to 3 (noncomatose patients) are usually operated on within 24 to 48 hours, because this has been shown to improve outcome (29, 30). Patients in grades 4 and 5 (comatose) are at a greater risk of poor outcome after early surgery (29, 30).

Deterioration caused by delayed ischemia is a result of cerebral vasospasm. Vasospasm is caused by the irritant effect of blood surrounding the blood vessels in the basal cistern. The vasospasm is probably induced partly by breakdown products of hemoglobin. Vasospasm is prophylactically treated with the calcium channel blocker nimodipine which has been shown to improve outcome in Hunt and Hess Grades 1–3. It is recommended that therapy with nimodipine 60 mg be started in the emergency department and continued for 21 days (5, 31, 32).

Hydrocephalus is a serious complication of subarachnoid hemorrhage. Acute obstructive hydrocephalus is associated with stupor or coma. Once confirmed by CT scan it requires immediate ventriculostomy. For patients with Hunt and Hess Grades 4 and 5 with hydrocephalus accompanied by a hematoma, surgical intervention may be lifesaving. Early neurosurgical consultation is imperative in all cases of subarachnoid hemorrhage.

Cerebellar Stroke

Cerebellar infarction and hemorrhage warrant separate consideration because of the rapid and life-threatening brainstem compression they may produce. Patients with cerebellar strokes may present with sudden onset of dizziness, nystagmus, vomiting, truncal ataxia, gait disturbance, gaze palsy, or stupor. The hematoma from a cerebellar hemorrhage or the swollen cerebellar hemisphere in an infarction can cause brainstem compression. Symptoms of brainstem compression include a decreasing level of consciousness, facial weakness, and gaze palsy. Patients may rapidly progress to coma and herniation, therefore prompt surgical decompression is indicated. All cerebellar strokes are neurosurgical emergencies requiring early neurosurgical consultation.

Transient Ischemic Attacks

Transient ischemic attacks (TIAs) are neurologic deficits that resolve within 24 hours, with most resolving within 30 minutes. Patients usually present for evaluation after the neurologic signs have ceased so that the diagnosis is often based on history. A TIA is a warning of an impending stroke. Approximately 20 to 30% of patients with TIA will subsequently have a stroke, with the greatest risk in the first few days or weeks (22).

Antiplatelet therapy with aspirin has a proven benefit in the prevention of stroke after TIA. Ticlopidine is another antiplatelet agent with a proven benefit but it is more expensive, takes several days for maximum effect, and requires careful hematologic monitoring because it can cause pancytopenia (22, 23). However, ticlopidine is useful for patients who are allergic to aspirin.

Anticoagulant therapy is not routinely recommended for patients after a TIA because there is no evidence to support its efficacy unless the embolism is from a cardiac source. Despite the lack of available data, some physicians recommend consideration of anticoagulation for patients with a pattern of crescendo TIAs, development of a TIA while taking aspirin, known high-grade carotid stenosis, and posterior circulation TIA (33).

All patients presenting with a possible TIA require a CT scan to exclude other etiologies of their neurologic symptoms. The remainder of the work-up is individualized based on the patient's characteristics and the type of TIA. Carotid Dopplers are a screening test, but Doppler results do not always correlate with angiographic results. Carotid endarterectomy has proven benefit in patients with TIA who have angiographically demonstrated carotid stenosis of 70% or greater, who are at low risk for surgical complications, and for whom a skilled surgeon is available (24). Patients with TIAs are at high risk for stroke, and management should be expedient. The need for close observation, rapid determination of etiology, and institution of appropriate therapy justify admission for patients with a recent TIA (less than 72 hours) or crescendo TIAs (34).

Neuroprotective Therapy

There are several different classes of agents being actively investigated which are thought to provide neuronal protection. In stroke, the disruption of blood flow results in numerous cellular and biochemical events. The ischemia causes energy failure which results in depolarization with release of neurotransmitters, the influx of intracellular calcium, and free radical release. With better understanding of the mechanisms of neuronal damage and death, new cytoprotective therapies are being studied. Many of these agents have been demonstrated to reduce stroke volume in animal models of stroke and are undergoing clinical trials. Several of these agents have shown promise in the treatment of traumatic brain injury and neurodegenerative diseases such as amyotrophic lateral sclerosis and Huntington's disease (35).

Excitatory Amino Acid Antagonists

The excitatory amino acid neurotransmitter glutamate is thought to have a crucial role in neuronal death and to be excitotoxic to the central nervous system. Drugs that antagonize excitatory amino acid transmission reduce infarct volume in experimental stroke models (36). Postsynaptic ionotropic glutamate receptors mediate rapid changes in postsynaptic membrane permeability to sodium or calcium. Two types of ionotropic receptors, *N*-methyl-D-aspartate (NMDA) and D-amino-3-hydroxyl-5-methyl-4-isoxazole (AMPA), have been studied. NMDA and AMPA receptor antagonists reduce infarct size in animals (37). Several NMDA receptor antagonists have been evaluated in safety trials, and some have progressed to efficacy trials. Noncompetitive NMDA antagonists include phencyclidine, ketamine, aptiganel hydrochloride (CNS 1102), dextrorphan, dextromethorphan, and remacemide desglycine (37). Competitive NMDA antagonists include CPP, *d*-CPPene, and selfotel (CGS 19755) (37). All competitive and noncompetitive NMDA receptor antagonists seem to have important similar dose-dependent psychomimetic side effects. Important cardiovascular side effects, such as hypotension and QT interval prolongation, have been noted in some agents.

Free Radical Scavengers

Biochemical studies have identified oxygen-free radicals as mediators of damage in stroke. Under hypoxic or ischemic conditions, mitochondria leak oxygen-free radicals, forming superoxide. Free radicals can react with and damage proteins, nucleic acids, and lipids. Most of the studies of free radicals in stroke have focused on lipid membrane damage. Free radicals cause the polyunsaturated fatty acids in the cell membrane to undergo lipid peroxidation, and the membrane structure is fragmented and disintegrates. Free radical scavengers which inhibit production of oxygen-free radicals are under investigation. Lazaroids, a class of compounds which include tirilazad mesylate, a 21-aminosteroid, have potent antioxident activity (36). In one study tirilazad significantly reduced infarct volumes in a temporary focal ischemia model, but it was less effective when ischemia was permanent (38). Animal models have shown that tirilazad is effective in subarachnoid hemorrhage by decreasing vasospasm, and in infarcts by reducing infarct size and peri-infarct edema (38). It is currently being tested in clinical trials for ischemic stroke and subarachnoid hemorrhage. Postischemic reperfusion introduces more oxygen into tissue, which leads to more free radicals and more lipid peroxidation and thus may exacerbate cellular damage. This has been postulated as an explanation for the narrow window of opportunity for beneficial reperfusion and why late reperfusion may actually be detrimental.

Gangliosides

Gangliosides are glycosphingolipids which are known to promote regeneration, sprouting, and survival of neurons. Changes in ganglioside composition occur during development and neuropathologic processes. In vitro the ganglioside GM-1 enhances cellular response to neuronotrophic factors and decreases glutamate-induced neuronotoxicity. The ganglioside GM-1 has improved neurologic function in animal models (39), and in preliminary clinical trials it has demonstrated an improvement in neurologic outcome (40, 41). Further larger clinical trials will be necessary to prove efficacy.

Leukocyte Inhibitors

Leukocytes have an adverse effect in the ischemic zone (42). Leukocyte activation occurs with ischemia and with reperfusion. Leukocytes may obstruct capillaries and release cytotoxic products, exacerbating CNS injury. Leukocyte activation may play an important role in reperfusion injury after thrombolytic therapy. Monoclonal antibodies that prevent leukocyte adhesion to the vascular endothelium have been developed. ICAM-1 is an intercellular adhesion molecule expressed on the vascular endothelium, and in an animal model, treatment with a monoclonal antibody against the ICAM-1 adhesion site increased the interval during which TPA was effective (43). These compounds may be effective on their own or may extend the window in which thrombolytics may be administered. Clinical trials are currently being conducted with the antibody to ICAM-1.

Conclusion

Major progress in the treatment of stroke is anticipated within the next several years. Many different therapies are currently being investigated. Promising results have been demonstrated for very early thrombolytic therapy for ischemic stroke. Preliminary studies indicate that low-molecular-weight heparin may have a benefit for ischemic stroke. Calcium channel blockers have been proven to be effective in treatment of subarachnoid hemorrhage. Neuroprotective agents including excitatory amino acid antagonists, free radical scavengers, gangliosides, and leukocyte inhibitors have shown promise in the treatment of all stroke types. Because of increased awareness that stroke is an emergency, patients are presenting sooner and being treated and enrolled in trials earlier. The future treatment of stroke probably will not be with a single therapy but with a combination of approaches. The role of the emergency department in rapid evaluation, diagnosis, and initiation of therapy for stroke will become increasingly important as early effective interventions are used.

References

1. American Heart Association. Heart and stroke facts. Dallas, TX: American Heart Association; 1993. p. 10–11.
2. Silver FL, Norris JW, Lewis AJ, Hachinski VC. Early mortality following stroke: A prospective review. Stroke 1984; 15:492–496.

3. Walker MD. Significance of stroke in society. In Stroke: Early pathophysiology and treatment. Summary of the fifth annual Decade of the Brain Symposium, Heros RC, Moderator. Stroke 1994; 25:1877–1881.
4. Camarata PJ, Heros RC, Latchaw RE. "Brain attack." The rationale for treating stroke as a medical emergency. Neurosurgery 1994; 34:144–158.
5. National Stroke Association Consensus Statement. Stroke: The first six hours. Emergency evaluation and treatment. Stroke Clin Updates 1993; 4:1–12.
6. American Heart Association. Guidelines for the management of patients with acute ischemic stroke. Stroke 1994; 25:1901–1914.
7. Brott T, Broderick J, Kothari R. Thrombolytic therapy for stroke. Curr Opin Neurol 1994; 7:25–35.
8. del Zoppo GJ. Thrombolytic therapy in acute ischemic stroke. J Stroke Cerebrovasc Dis 1994; 4:552–558.
9. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemisphere stroke: the European Cooperative Acute Stroke Study (ECASS). JAMA 1995; 274:1017–1025.
10. Multicenter Acute Stroke Trial-Italy (MAST-I) Group. Randomized controlled trial of streptokinase, aspirin and combination of both in treatment of acute ischemic stroke. Lancet 1995; 346:1509–1514.
11. The Multicenter Acute Stroke Trial-Europe Study (MAST-E) Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. N Engl J Med 1996; 335: 145–150.
12. Donnan GA, Davis SM, Chambers BR, et al. Trials of streptokinase in severe acute ischemic stroke. Lancet 1995; 345:578–579.
13. The National Institute of Neurologic Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333: 1581–1587.
14. Duke RJ, Block RF, Turpie AGG, et al. Intravenous heparin for the prevention of stroke progression in acute partial stable stroke. A randomized controlled trial. Ann Intern Med 1986; 105:825–828.
15. Haley EC, Kassell NF, Torner JC. Failure of heparin to prevent progressing ischemic infarction. Stroke 1988; 19:10–14.
16. Cerebral Embolism Study Group. Immediate anticoagulation of embolic stroke: A randomized trial. Stroke 1993; 14:668–676.
17. Cerebral Embolism Study Group. Immediate anticoagulation of embolic stroke: Brain hemorrhage and management options. Stroke 1984; 15:779–789.
18. Chamorro A, Vila N, Saiz A, et al. Early anticoagulation after large cerebral embolic infarction: A safety study. Neurology 1995; 45:861–865.
19. Hirsh J, Levine MN. Low molecular weight heparin. Blood 1992; 79:1–17.
20. Kay R, Wong KS, Yu YL, et al. Low-molecular-weight heparin for the treatment of acute ischemic stroke. N Engl J Med 1995; 333:1588–1593.
21. Adams HJ, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter trial. TOAST. Trial of Org 10172 in acute stroke treatment. Stroke 1993; 24:35–41.
22. Barnett HJ, Eliasziw M, Meldrum HE. Drugs and surgery in the prevention of ischemic stroke. N Engl J Med 1995; 332:238–248.
23. Meyer FB, Piepgras DC, Sundt TM Jr, Yanaghara T. Emergency embolectomy for acute occlusion of the middle cerebral artery. J Neurosurg 1985; 62:639–647.
24. North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325: 445–453.
25. Meyer FB, Sundt TM Jr, Piepgras DG, et al. Emergency carotid endarterectomy for patients with acute carotid occlusion and profound neurologic deficits. Ann Surg 1986; 203:82–89.
26. Kaneko M, Tanaka K, Shimada T, et al. Long term evaluation of ultra-early operation for hypertensive intracerebral hemorrhage in 100 cases. J Neurosurg 1983; 58: 838–842.
27. Kanno T, Sano H, Shinomiya Y, et al. Role of surgery in hypertensive intracerebral hematoma: A comparison of 305 nonsurgical and 154 surgical cases. J Neurosurg 1984; 61:1091–1099.
28. Kopitnik TA, Kaufman HH. The future prospects of innovative treatment of intracerebral hemorrhage. Neurosurg Clin N Am 1992; 3:703–707.
29. Hunt RC, Hess RN. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg 1968; 8:1920–1968.
30. Haley EC Jr, Kassell NF, Torner JC, et al. The international cooperative study on the timing of aneurysm surgery: The North American experience. Stroke 1992; 23: 205–214.
31. Phillippon J, Grob R, Dagreau F, et al. Prevention of vasospasm in subarachnoid hemorrhage: A controlled study with nimodipine. Acta Neurochir 1986; 82:110–114.
32. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage. British aneurysm nimodipine trial. Br Med J 1989; 298:636–642.
33. Feinberg WM, Albers GW, Barnett HJ, et al. American Heart Association. Guidelines for the management of transient ischemic attacks. Circulation 1994; 89:2950–2965.
34. Henneman PL, Lewis RJ. Is admission medically justified for all patients with acute stroke or transient ischemic attack? Ann Emer Med 1995; 25:458–463.
35. Trembly B. Clinical potential use of neuroprotective agents. A brief overview. Ann NY Acad Sci 1995; 15:1–20.
36. Fisher M, Bogousslavsky J. Evolving toward effective therapy for acute ischemic stroke. JAMA 1993; 270: 360–364.
37. Muir KW, Lees KR. Clinical experience with excitatory amino acid antagonist drugs. Stroke 1995; 26:503–513.
38. Schmidley JW. Free radicals in central nervous system ischemia. Stroke 1990; 21:1086–1090.
39. Skaper SD, Leon A. Monosialogangliosides, neuroprotection and neuronal repair processes. J Neurotrauma 1992; 9 (Suppl):S507–516.
40. Argentino C, Sacchetti ML, Toni D, et al. GM1 ganglioside therapy in acute ischemic stroke. Stroke 1989; 20:1143–1149.
41. The Sygen Acute Stroke Study (SASS). Ganglioside GM1 in acute ischemic stroke. Stroke 1994; 25:1141–1148.
42. Fisher M. Potentially effective therapies for acute ischemic stroke. Eur Neurol 1995; 35:3–7.
43. Bowes MP, Rothlein R, Fagan SC, et al. Monoclonal antibodies preventing leukocyte activation reduce experimental neurologic injury and enhance efficacy of thrombolytic therapy. Neurology 1995; 45:815–819.

The Evaluation and Treatment of Seizures in the Emergency Department

Andy Jagoda, M.D.,[1] and Lynne Richardson, M.D.[2]

Abstract

One to two percent of visits to the emergency department are due to seizures. These patients may require aggressive stabilization and resuscitation and concurrent implementation of diagnostic testing, monitoring, and pharmacologic interventions. Seizures are usually a manifestation of an underlying pathology which requires thorough evaluation, including a careful history, physical examination, laboratory work-up, and electroencephalographic and neuroimaging studies as dictated by clinical suspicion. The evaluation and treatment of seizures in the emergency department must be comprehensive, including giving consideration to the patient's medical and social resources. **Key Words:** seizures, status epilepticus, alcohol withdrawal, drug overdose, febrile seizures.

Seizures account for 1 to 2% of emergency department (ED) visits (1). The focus of ED management is to stabilize the patient, identify and treat life-threatening conditions, and to provide acceptable follow-up. In approaching the patient with a seizure, the emergency physician is often constrained by the paucity and reliability of historical information and by the limited resources available to some patients in obtaining the follow-up care that their condition might require. Consequently, multiple factors must be carefully weighed when deciding the best approach to the diagnostic testing and therapeutic interventions initiated in the ED. Seizures are frequently the result of an underlying process (termed secondary or symptomatic seizures). Identifying reversible etiologies is one of the primary goals in emergency management (see Table 1). A careful history, physical examination, and selective use of laboratory studies and neuroimaging are necessary to guide management.

Differential Diagnosis

There are several conditions that can mimic or be misinterpreted as an epileptic seizure. These conditions include convulsive syncope, with or without cardiac dysrhythmias; decerebrate posturing; psychogenic events; dystonia; and migraine headaches. An in-depth discussion of these entities is beyond the scope of this paper, but brief mention of several key points is useful because misdiagnosis can have significant impact on patient treatment (2–4).

Up to 40% of patients who have syncope will manifest some component of motor activity, most often involving tonic extension of the trunk or myoclonic jerks of the extremities (5). This will usually occur if the patient is kept in a sitting position (6). These events are termed convulsive syncope and usually not associated with tonic-clonic movements, tongue biting, cyanosis, incontinence, or postictal amnesia.

Cardiac dysrhythmias can result in hypotension with central nervous system (CNS) hypoper-

---

From the Department of Emergency Medicine, Mount Sinai School of Medicine, New York. [1]FACEP, Associate Professor of Emergency Medicine, and [2]FACEP, Director of Residency Training. Address correspondence to Andy Jagoda, M.D., Box 1149, Mount Sinai School of Medicine, Department of Emergency Medicine, New York, NY 10029.

TABLE 1
Etiologies of Secondary Seizures

- Tumors
- Vascular event
  - Subarachnoid hemorrhage
  - Subdural hemorrhage
  - Epidural hemorrhage
  - Stroke
  - Vasculitis
- Infection
  - Meningitis
  - Encephalitis
  - Abscess
- Metabolic
  - Hypoglycemia[a]
  - Hyponatremia[b]
  - Hypomagnesemia[c]
  - Hypocalcemia
- Toxic: Consider the following in overdose.
  - Cocaine and sympathomimetics
  - Tricyclic antidepressants
  - Anticholinergics
  - Theophylline
  - Isoniazid
- Eclampsia

[a] The most common metabolic cause of seizures.

[b] A rare cause of seizures except in infants <6 months of age.

[c] Rarely an isolated cause of seizures; possibly facilitates seizures, especially in malnourished patients, e.g., alcoholics.

fusion which results in symptoms that can be confused with convulsive or nonconvulsive seizures (7). A careful history will often identify previous cardiac symptoms such as palpitations, lightheadedness, or diaphoresis. The diagnosis frequently requires careful coordination with the patient's primary care physician for Holter monitoring, continuous cardiac loop monitoring, and head-up tilt-table testing.

Decerebrate posturing has been mistaken for tonic seizures, which results in misdiagnosis and delay in providing potentially life-saving interventions for increased intracranial pressure (3). It should be remembered that tonic seizures are rare in adults, and when they do occur they are usually of short duration with upper extremity abduction. Decerebrate posturing results in both upper and lower extremity extension.

Psychogenic seizures refer to nonepileptic events that are functional in etiology (8). They are often long lasting with no postictal period, and patients often, but not always, recall events that occur during the seizure. Incontinence or physical injury can occur, but are not common. Classically, patients with psychogenic motor events have asynchronous movements of their extremities, forward pelvic thrusting movements, head turning from side to side, and avoidance of noxious stimuli, although no one feature is pathognomonic (9). Diagnostically, patients with psychogenic motor events do not develop metabolic acidosis despite prolonged seizure activity, nor do they manifest an elevation in serum prolactin levels (10).

Emergency Department Evaluation

The history begins with a careful description of the event and its surrounding circumstances with documentation of the preliminary symptoms, progression of the clinical pattern, duration of the event including the postictal period, and presence of incontinence or biting of the tongue. Every effort must be made to obtain a clear description of the event(s) from witnesses. Patients who seize for more than 30 minutes or who have had repeated convulsions without a return to baseline are in status epilepticus and need immediate interventions, because prognosis worsens in relation to the duration of the event.

In patients with epilepsy, any changes in the character of the seizure, such as frequency or clinical features must be investigated. Noncompliance with anticonvulsants is the most common cause of recurrent seizures in this group of patients. The use and doses of anticonvulsants and other medications must be ascertained. Seizure disorders may be exacerbated by several stressors, such as fatigue, pregnancy, or systemic infection. Identification of the stressors may explain an event and become the focus of management.

Seizure activity tends to prompt aggressive interventions, but it is critical to stress the importance of taking the time to carefully observe the patient and to perform a physical examination. Obtain an accurate set of vital signs, including a rectal temperature. Assess the mental status, skin color, and pupil position and reactivity. If the patient is actively convulsing, describe the motor activity. Look for "automatisms," which are repetitive actions such as lip smacking, swallowing, chewing, or fumbling. Automatisms are frequently seen in complex partial seizures and may be the only indicator that there is ongoing seizure activity.

Seizures resulting from drug overdose may be suggested by the presence of a toxidrome as seen in anticholinergic, sympathomimetic, or tricyclic ingestions (11, 12). Hypertension with bradycardia may indicate an intracranial catastrophe, whereas fever may be the manifestation of a CNS infection (although seizures may independently result in elevated temperatures from muscular hyperactivity or central deregulation) (13, 14). Irregular heart rate or carotid bruits may indicate a stroke, which is the most common cause of new-onset seizures in the elderly (15).

Evaluate the patient for both soft tissue and skeletal trauma, especially head trauma and tongue lacerations. Seizure activity has been reported to directly cause both dislocations and fractures. Posterior shoulder dislocations are extremely rare and, when present, prompt suspicion that a seizure has occurred (16). Seizure-induced fractures are rare, occurring in less than 0.6% of events, and most often involve the humerus, thoracic spine, and femur; 60 to 80% of these cases are missed initially (17, 18).

Perform a complete neurologic examination identifying focal deficits which may represent an old lesion, new intracranial pathology, or reversible postictal neurologic compromise (Todd's paralysis). In a new Todd's paralysis, the physician must rule out a new structural lesion. Other physical findings suggesting that a patient has had a seizure include hyperreflexia and extensor plantar responses, both of which should resolve during the immediate postictal period.

Document the patient's mental status, recruiting the assistance of persons familiar with the patient. Postictal confusion usually resolves over several hours, and the failure to gradually improve must prompt a search for other causes (see Table 2). In particular, nonconvulsive status epilepticus can present with subtle behavioral changes which can be easily discounted unless the clinician maintains a high index of suspicion (2, 19).

Laboratory Studies

The laboratory tests indicated in the ED for patients presenting after having had a seizure for the first time, who are alert and oriented and who have no clinical findings, is controversial (20–24). At a minimum, these patients need tests for serum glucose and electrolyte levels, and women of child-bearing age require a pregnancy test (20–22). A drug-of-abuse screen should be considered (23). All other tests have a very low yield in this group of patients, and there are no prospective studies at this time to support more in-depth testing in the ED, such as tests for phosphate, calcium, or magnesium levels. However, patients who are receiving dialysis, malnourished, or taking diuretics, or who have underlying significant medical disorders, need a complete blood cell count, blood urea nitrogen, serum creatinine, calcium, phosphate, and magnesium, and a urinalysis.

TABLE 2

Differential Diagnosis of Altered Mental Status in a Patient Who Has Had a Seizure

Postictal state
Nonconvulsive status or subtle convulsive status
Hypoglycemia
CNS infection
CNS vascular event
Drug toxicity
Psychiatric disorder

Patients with a known seizure disorder, who have a "typical" event while taking medications, but who are asymptomatic, alert, and oriented in the ED, only need a test for a serum anticonvulsant level, unless they have another underlying disease such as diabetes that could result in a metabolic derangement. In these patients, it is important to investigate potential precipitants, such as infections or new medications, which might have contributed to the event.

Patients who are in convulsive status epilepticus, and those who are not actively convulsing but who are persistently postictal, require comprehensive diagnostic testing which includes a determination of serum glucose, electrolyte, urea nitrogen, creatinine, magnesium, phosphate, and calcium levels; a complete blood cell count; a pregnancy test in women of child-bearing age; determination of antiepileptic drug levels; liver function tests; and a drug-of-abuse screen (25).

TABLE 3

Treatment of Status Epilepticus

Stabilization
Protect the patient; do not place anything in the mouth.
Secure the airway; intubate if evidence of ineffective respirations/oxygenation.
Establish intravenous access with nondextrose solution.
Activated charcoal if drug overdose is considered.
Initial interventions
Dextrose, if hypoglycemic, 50 cc of 50% glucose; in children 2 cc/kg of 25% glucose; thiamine, 100 mg i.v. or i.m. before glucose, if malnourished.
Ceftriaxone, 100 mg/kg up to 2 g i.v., if meningitis is suspected.
Lorazepam, 0.1 mg/kg at 2 mg/min to a maximum of 10 mg; or diazepam, 0.2 mg/kg at 5 mg/min to a maximum of 20 mg.
Phenytoin, 18 mg/kg i.v. at 25 mg/kg in patients with cardiac disease, otherwise 50 mg/min; in children, 1 mg/kg/min OR fosphenytoin, 30 mg/kg (18 mg/kg of phenytoin equivalent units) i.v. at 150 mg/min.
Persisting seizures
Give additional i.v. phenytoin, or the phosphate ester, up to 30 mg/kg OR Phenobarbital, 20 mg/kg at 100 mg/min i.v.
Refractory seizures
Pentobarbital, 5 mg/kg i.v. at 25 mg/min followed by 0.5–3 mg/kg/hr OR benzodiazepine infusion: Midazolam i.v. bolus of 200 μg/kg followed by 1–10 μg/kg/min; lorazepam, 0.3–10 mg/hr.

An arterial blood gas analysis (ABG) obtained in a patient who is convulsing will show an anion gap metabolic acidosis which is usually secondary to lactic acidosis (26). The anion gap acidosis should resolve within 1 hour after the seizure ends; persistence after 1 hour suggests the presence of one of the other causes of anion gap acidosis such as methanol, ethylene glycol, or salicylate toxicity. The ABG will also provide information regarding hypercarbia and oxygenation. If carbon monoxide poisoning is suspected, a carboxyhemoglobin level should be determined.

Rhabdomyolysis, which is a rare consequence of a seizure, may be diagnosed if the urine tests positive for blood in the absence of red blood cells on the microscopic examination. A test to determine serum creatine phosphokinase level is indicated in these cases (27).

Cardiac monitoring for dysrhythmias is an important part of every resuscitation. An electrocardiogram (ECG) should be obtained at the earliest possible moment, because it may help reveal evidence of drug overdose.

Lumbar Puncture

A lumbar puncture is strongly considered in those patients who are in status epilepticus, who have an unresolving postictal state, fever, headache, meningeal signs, a positive HIV history, or who are otherwise immunocompromised. There are no prospective studies that support performing a lumbar puncture as part of the diagnostic evaluation in the ED on patients who are alert, oriented, asymptomatic, and not immunocompromised even if the seizure is a first-time event. In one retrospective series of 503 cases of meningitis in children 2 months to 15 years of age there was no case of occult bacterial meningitis manifesting solely as a simple seizure (28).

Neuroimaging

The indications and timing of computed tomography (CT) of the head, especially in patients with a first-time seizure, are controversial (29–31). Of patients with a first-time seizure, 3 to 41% have an abnormal head CT (23). In one retrospective review, 22% of patients with a first-time seizure, whose neurologic examinations had normal results, had an abnormal head CT (23). The question remains whether identifying the abnormality in patients with nonfocal neurologic examinations who are evaluated in the ED has an impact on outcome. A head CT should be strongly considered in the ED whenever an acute intracranial process is suspected in patients with a history of acute head trauma, malignancy, immunocompromise, fever, persistent headache, or anticoagulation, or a new focal neurologic examination (32).

Electroencephalography

An urgent electroencephalogram (EEG) in the ED is recommended for those patients with persisting altered mental status in whom subtle convulsive or nonconvulsive status epilepticus is suspected. An EEG is also required when a patient's motor activity has been suppressed by either paralysis or barbiturate coma and assessment of ongoing seizure activity is needed.

Prehospital Management

Prehospital management of the patient who is convulsing centers on securing the airway, maintaining oxygenation, obtaining intravenous access, and protecting the patient from injury. Fortunately most seizures are of short duration and little else usually needs to be done. The use of a padded tongue blade is contraindicated because it may induce emesis or break a tooth; a nasal trumpet can be used to help maintain the airway when needed. These patients require immediate determination of blood sugar or, if that test is not available, dextrose can be given empirically although in general it is best to avoid osmotic loads when possible (33). If the seizure continues for more than several minutes, lorazepam is given, 2 mg intravenously every minute up to a maximum of 10 mg; both intramuscular and rectal routes have been used successfully when intravenous access was not available. Diazepam, 5 mg intravenously every minute up to a total of 20 mg, also can be used, but its shorter duration of action and its water insolubility makes it less desirable (34). The patient is transported via an advanced life support unit, when available, to the closest ED.

Patients who have a known seizure disorder, experience a "typical" event, and are asymptomatic do not necessarily require transport to the hospital if they are competent and are comfortable with their disorder. These patients should be advised to contact their primary care provider as soon as possible. All other asymptomatic patients who have had a seizure should be transported to an ED for evaluation. It is unlikely that this group of patients will experience a second event during transport and thus can be transported by a basic life support unit if transport times are reasonably short (35).

Management of Status Epilepticus

Management of status epilepticus must take into consideration the treatable etiologies (Table 1), because it will be difficult to control the seizures unless the precipiting causes are addressed. Therefore a comprehensive approach must be taken that concomitantly ensures oxygenation and intravenous access, obtains diagnostic studies, and initiates pharmacologic interventions.

Oxygenation can be monitored with pulse oximetry. However pulse oximetry does not monitor the efficiency of respirations or presence of hypercarbia. If, at any time, breathing appears compromised, rapid sequence intubation is recommended using succinylcholine and protective measures against increased intracranial pressure. Long-acting paralyzing agents are contraindicated because they mask clinical findings. Intravenous access is best secured with a nondextrose solution because dextrose will precipitate phenytoin if administered concurrently. Obtain a rapid bedside serum glucose level and if it is less than 80 mg/dL, or if a rapid dextrose determination is unavailable, administer 50 cc of 50% dextrose intravenously in adults, or 2 mL/kg of 25% dextrose in children. Thiamine, 100 mg, is recommended with dextrose boluses in patients who appear malnourished or abuse alcohol. In certain situations in which infection is suspected, early consideration must be given to empiric antibiotic treatment because obtaining a head CT and performing a lumbar puncture most likely will be delayed pending patient stabilization. Likewise, early administration of activated charcoal, 1 g/kg, is recommended in cases of suspected overdose.

Benzodiazepines are considered the best first-line drugs in managing status epilepticus, although both phenytoin and phenobarbital have been used (25, 36). Diazepam, 0.2 mg/kg at 5 mg/min, and lorazepam, 0.1 mg/kg at 2 mg/min, are equally effective in terminating seizures; lorazepam has the advantage of a much smaller volume of distribution with anticonvulsant activity of several hours versus 20 minutes for diazepam (34, 37). At the same time that a benzodiazepine is given, intravenous phenytoin loading, 18 mg/kg, is started (see below). The dose can be increased up to 30 mg/kg if the seizures do not stop after the initial load (25, 38). Phenytoin loading can result in infusion site irritation, hypotension, confusion, and ataxia. Infusions are best administered through a large vein to minimize sclerosis from the alkaline pH. The infusion rate should be no faster than 25 mg/min in patients with cardiac disease to minimize cardiovascular complications, and 50 mg/min in other patients (39).

A new preparation of phenytoin, fosphenytoin, which is a phosphate ester of phenytoin, has recently become available (40). Fosphenytoin is water soluble obviating the need for the propylene glycol vehicle, because it does not precipitate with glucose. Fosphenytoin is less of a tissue irritant than the phenytoin/propylene glycol preparation, with pruritis and paresthesias the most common side effects. There are minimal cardiotoxic effects, although hypotension has been reported with rapid infusions. Blood pressure should be carefully monitored, especially in patients with underlying cardiovascular disease. Fosphenytoin has a peak serum level within 30 minutes after intramuscular administration and at 6 minutes after intravenous loading. The loading dose is 18 mg/kg. In emergencies, when given intravenously, the recommended infusion rate is 150 mg/min (40).

Phenobarbital, 20 mg/kg at 100 mg/min, is recommended for those patients who continue to seize despite benzodiazepine and phenytoin loading. At the same time, the resuscitation effort should be reassessed to ensure that the patient is properly oxygenated and is not hypoglycemic, that intravenous lines are functioning, and that phenytoin was not administered in a dextrose solution.

After phenobarbital, the two options most commonly used in cases of refractory status epilepticus are pentobarbital anesthesia or continuous benzodiazepine infusion. Pentobarbital, 5 mg/kg followed by an infusion of 0.5 to 3 mg/kg/hr, is effective in suppressing electrical discharges. Pentobarbital can compromise cardiovascular status, and its use necessitates EEG monitoring because motor activity will be suppressed (25, 38, 41).

There are reports supporting the use of intravenous infusions of lorazepam, 0.3–9 mg/hr (42); midazolam, 0.5 mg/hr (43); and diazepam, 8 mg/hr (44). However, there are no controlled studies at this time to help assess the value of these infusions compared with other third-line anticonvulsants. Some evidence questions the utility of these infusions because there may be a loss of γ-aminobutyric acid-mediated inhibition (the anticonvulsant mechanism of the benzodiazepines) after prolonged seizure activity (45).

Other drugs that have been used in the management of status epilepticus include lidocaine, 1–2 mg/kg intravenously (46); chloral hydrate, 30 mg/kg rectally (47); paraldehyde, 5–10 mL in a 2:1 dilution with mineral oil, rectally (48); and isoflurane anesthesia (49). All of these drugs have been described as effective in case series but have not been validated in controlled trials.

Special Situations

Initiation of Anticonvulsant Therapy in the ED for First-Time Seizures

The decision to initiate anticonvulsant therapy in the ED should always be made in conjunction with the patient's primary care provider or neurologist. The decision for therapy is based on the underlying cause of the seizure, the results of the head CT or MRI, and an EEG. All of these data are rarely available before discharge from the ED, consequently the decision to initiate therapy must be based on the predicted risk for seizure recurrence.

The chances of a patient having a recurrent event after one unprovoked seizure varies depending on the patient's age and the underlying etiology of the seizure (50–52). Seizure etiology combined with EEG findings are the best predictors of recurrence; when no etiology is identified and the EEG findings are normal, the recurrence rate is 24% at 2 years (50). Patients who have structural lesions on CT or patients with focal seizures that secondarily generalize have a risk of recurrence of up to 65% and are the group of patients that probably benefit from initiating anticonvulsant therapy in the ED (50).

Alcohol Withdrawal Seizures

Alcohol withdrawal seizures occur as the result of acute changes in central nervous system alcohol levels, usually between 6 and 48 hours after cessation of drinking. Withdrawal seizures are usually generalized events that can be multiple but rarely persist for more than 12 hours. The diagnosis is based on history of recurrent events clearly related in time to cessation of drinking. Consequently, a first-time withdrawal seizure must be worked up as any first-time seizure (53). Withdrawal seizures are managed with benzodiazepines and supportive care. Phenytoin has been clearly shown to have no role in the management of withdrawal seizures (54, 55).

Seizures and Severe Brain Injury

An estimated 10 to 15% of patients with severe brain injury (Glasgow Coma Scale < 8) will develop a seizure disorder (56); however, there is no good evidence that initiating anticonvulsant therapy early in the management of severe brain injury will prevent the development of epilepsy. Fourteen percent of patients with severe brain injury will seize in the first week postinjury (57). The incidence of posttraumatic seizures in the first week is decreased to less than 4% by the early use of phenytoin; however, after the first week, there is no statistical difference in seizure incidence whether or not patients are treated with phenytoin (57).

Management of Febrile Seizures

Febrile seizures are events that occur between 6 months and 5 years of age, are associated with fever, and have no identifiable underlying cause. Simple febrile seizures are generalized tonic clonic events with no focality, lasting less than 15 minutes with a short postictal period. Complex febrile seizures last longer than 15 minutes, occur in a series, have a focal onset, or a prolonged postictal period.

The management of simple febrile seizures focuses on parental education. A diagnostic work-up, even for first-time events, is not indicated when they occur in children older than 18 months who have not been receiving antibiotics (58, 59). Diagnostic studies instead are guided by general fever protocols. However, in patients less than 18 months of age the signs of meningitis may be subtle or absent, and thus lumbar puncture must be strongly considered. Laboratory evaluation of serum electrolytes, calcium, phosphorous, magnesium, glucose, complete blood cell count, or neuroimaging are not routinely necessary in patients with simple febrile seizures (58, 59). Complex febrile seizures necessitate a complete diagnostic work-up looking for underlying precipitating etiologies.

Management of Elevated Anticonvulsant Serum Levels and Intoxications

Current recommendations for the management of epilepsy emphasize the use of monotherapy with increasing single-drug dosing to the point of seizure control or clinical toxicity (60).

Serum drug levels are therefore used only as a guide to therapy and must be interpreted in the context of the patient's clinical status. In addition, drug levels may vary depending on the patient's dosing schedule. For example, single dosing of phenytoin may result in a peak serum level that is two to three times that of the trough (61). Asymptomatic patients with elevated serum levels must be carefully assessed; decisions to alter anticonvulsant therapy are best made in conjunction with the patient's primary care provider.

Anticonvulsant intoxications primarily involve the nervous system presenting with altered mental status, ataxia, nystagmus, and very rarely, seizures. Respiratory depression can also occur. Carbamazepine can produce signs and symptoms of anticholinergic poisoning. Carbamazepine, phenobarbital, and valproic acid can compromise cardiovascular status in massive overdose. Carbamazepine's tricyclic structure was once thought to portend significant cardiovascular complications whereas in actuality they rarely occur (62–65). Phenytoin ingestions are unlikely to produce cardiodepressant effects even in severe overdose (66). Reports of sudden cardiac death in patients receiving the intravenous form of the drug were most likely the result of rapid infusion of propylene glycol, phenytoin's diluent (67–69).

Patients who have received overdoses and who are at greatest risk for complications are those with chronic exposures, and those presenting with an abnormal ECG, profound obtundation, decreased respirations, or seizures. On arrival at the ED, patients suspected of having, or developing, anticonvulsant toxicity require that their airway and intravenous access be secured, an ECG obtained, and serum drug level determined. Patients are best decontaminated using gastric lavage, if the ingestion occurred less than 2 hours earlier, followed by oral administration of activated charcoal, 1 g/kg, plus a cathartic. Multidose charcoal has been beneficial in enhancing the elimination of phenytoin (70–72), carbamazepine (73, 74), phenobarbital (74), and valproic acid (75). Repeat doses of activated charcoal, without a cathartic, are given every 2 to 4 hours, if bowel sounds are present, for four doses or until the patient's plasma levels begin to decline. Elimination of phenobarbital can also be hastened by alkalinizing the patient's urine. Severe phenobarbital overdoses may require hemodialysis (76).

Plasma concentrations serve as an important assessment tool after anticonvulsant overdose and should be documented every 2 hours until they peak; once a downward trend is achieved, levels can be obtained every 8 to 12 hours. When levels approach the therapeutic range, reinstitution of therapy may be necessary for patients with known seizure disorders.

Conclusion

The ED approach to the seizure patient begins with a careful assessment of the event with consideration given to the various disorders that can mimic epileptic seizure activity. The history, physical, and diagnostic tests are obtained to elucidate the seizure's etiology and to guide management. Consultation should be made with the patient's primary care physician or neurologist to coordinate therapeutic interventions and follow-up. Disposition from the ED must take in to consideration the patient's social situation, resources, and compliance. All patients who have had a seizure must be advised not to drive and to avoid placing themselves in potentially dangerous situations.

References

1. Krumholz A, Grufferman S, Orr S, Stern B, Seizures and seizure care in an emergency department. Epilepsia 1989; 30:175–181.
2. Lee S. Nonconvulsive status epilepticus: Ictal confusion in later life. Arch Neurol 1985; 42:778–781.
3. Haines S. Decerebrate posturing misinterpreted as seizure activity. Am J Emerg Med 1988; 6:173–177.
4. Howell S, Owen L, Chadwick D. Pseudostatus epilepticus. Q J Med 1989; 71:507–519.
5. Lin J. Convulsive syncope in blood donors. Ann Neurol 1982; 11:525–528.
6. Ziegler D, Lin J, Bayer W. Convulsive syncope: Relationship to cerebral ischemia. Trans Am Neurol Assoc 1978; 103:150–154.
7. Linzer M, Grubb B, Simon H, Ramakrishnan L, Bromfield E, Estes N. Cardiovascular causes of loss of consciousness in patients with presumed epilepsy: A cause of increased sudden death rate in people with epilepsy. Am J Med 1994; 96:146–154.
8. Ozkara C, Dreifuss R. Differential diagnosis in pseudoepileptic seizures. Epilepsia 1993; 34:294–299.
9. Gates J, Ramani V, Whalen S, Loewenson R. Ictal characteristics of pseudoseizures. Arch Neurol 1985; 42: 1183–1187.
10. Riggio S. Psychogenic seizures. Emerg Med Clin North Am 1994; 12:1001–1012.
11. Alldredge B, Lowenstein D, Simon R. Seizures associated with recreational drug abuse. Neurology 1989; 39: 1037–1039.
12. Olson K, Kearney T, Dyer J, et al. Seizures associated with poisoning and drug overdose. Am J Emerg Med 1993; 11:565–568.
13. Simon R. Physiologic consequences of status epilepticus. Epilepsia 1985; 26(Suppl 1):58–66.
14. Aminoff M, Simon R. Status epilepticus: Causes, clinical features and consequences in 98 patients. Am J Med 1980; 69:657–666.

15. National Stroke Association. Seizures after stroke. Stroke Clin Updates 1994; 5:5–8.
16. Pear B. Bilateral posterior fracture dislocation of the shoulder: An uncommon complication of a convulsive seizure. N Engl J Med 1970; 283:135–136.
17. Finelli P, Cardi J. Seizures as a cause of fracture. Neurology 1989; 39:858–860.
18. McCullen G, Brown C. Seizure-induced thoracic burst fractures: A case report. Spine 1994; 19:77–79.
19. Tomson T, Lindbom U, Nilsson B. Nonconvulsive status epilepticus in adults: Thirty-two consecutive patients from a general hospital population. Epilepsia 1992; 33: 829–835.
20. American College of Emergency Physicians. Clinical policy for the initial approach to patients presenting with a chief complaint of seizure, who are not in status epilepticus. Ann Emerg Med 1993; 22:875–883.
21. Turnbull T, Vanden Hoed T, Howes D, Eisner R. Utility of laboratory studies in the emergency department patient with a new-onset seizure. Ann Emerg Med 1990; 19:373–377.
22. Powers R. Serum chemistry abnormalities in adult patients with seizures. Ann Emerg Med 1985; 14:416–420.
23. Henneman P, DeRoos F, Lewis R. Determining the need for admission in patients with new-onset seizures. Ann Emerg Med 1994; 24:1108–1114.
24. Tardy B, LaFond P, Convers P, et al. Adult first generalized seizure: Etiology, biological tests, EEG, CT scan, in an ED. Am J Emerg Med 1995; 13:1–5.
25. Working Group on Status Epilepticus. Treatment of convulsive status epilepticus: Recommendations of the Epilepsy Foundation of America's working group on status epilepticus. JAMA 1993; 270:854–859.
26. Orringer C, Eustace J, Wunsch C, et al. Natural history of lactic acidosis after grand-mal seizures. N Engl J Med 1977; 297:796–799.
27. Singhal P, Chugh K. Myoglobinuria and renal failure after status epilepticus. Neurology 1978; 28:200–201.
28. Green S, Rothrock S, Clem K, Zurcher R, Mellick L. Can seizures be the sole manifestation of meningitis in febrile children? Pediatrics 1993; 92:527–534.
29. Reinus W, Wippold F, Erickson K. Seizure patient selection for emergency computed tomography. Ann Emerg Med 1993; 22:1298–1303.
30. Russo L, Goldstein K. The diagnostic assessment of single seizures: Is cranial computed tomography necessary? Arch Neurol 1983; 40:744–746.
31. Ramirez-Lassepas M, Cipolle R, Morillol, Gumnit R. Value of computed tomographic scan in the evaluation of adult patients after their first seizure. Ann Neurol 1984; 15:536–543.
32. American Academy of Neurology. Neuroimaging in the emergency patient presenting with seizures. Ann Emerg Med 1996; 28:114–118.
33. Sands C, Jagoda A, Vukich D. Fluids in prehospital care: crystalloid versus dextrose solutions, is there a difference? J Emerg Med 1994; 12:803–809.
34. Treiman D. Pharmacokinetics and clinical use of benzodiazepines in the management of status epilepticus. Epilepsia 1989; 30:4–10.
35. Abarbanell N. Prehospital seizure management: Triage criteria for the advanced life support rescue team. Am J Emerg Med 1993; 11:210–214.
36. Jagoda A, Riggio S. Refractory status epilepticus in adults. Ann Emerg Med 1993; 22:1337–1348.
37. Leppik I, Derivan A, Homan R, et al. Double-blind study of lorazepam and diazepam in status epilepticus. JAMA 1983; 249:1452–1453.
38. Osorio I, Reed R. Treatment of refractory generalized tonic clonic status epilepticus with pentobarbital anesthesia after high dose phenytoin. Epilepsia 1989; 30: 464–471.
39. Donovan P. Phenytoin administration by constant intravenous infusion: Selective rates of administration. Ann Emerg Med 1991; 20:139–142.
40. Wilder BJ (ed). The use of parental antiepileptic drugs and the role for Fosphenytoin. Neurology 1996; 46:S1–S28.
41. Van Ness P. Pentobarbital and EEG burst suppression in treatment of status epilepticus refractory to benzodiazepines and phenytoin. Epilepsia 1990; 31:61–67.
42. Labar D, Ali A, Root J. High-dose intravenous lorazepam for the treatment of refractory status epilepticus. Neurology 1994; 44:1400–1403.
43. Parent J, Lowenstein D. Treatment of refractory generalized status epilepticus with continuous infusion of midazolam. Neurology 1994; 44:1837–1840.
44. Bell H, Bertino J. Constant diazepam infusion in the treatment of continuous seizure activity. Drug Intell Clin Pharm 1984; 18:965–970.
45. Kapur J, Lothman E, DeLorenzo R. Loss of GABA receptors during partial status epilepticus. Neurology 1994; 44:2407–2408.
46. Pascual J, Sedano M, Polo J, et al. Intravenous lidocaine for status epilepticus. Epilepsia 1988; 29:584–589.
47. Lampl Y, Eshel Y, Gilad R, et al. Chloral hydrate in intractable status epilepticus. Ann Emerg Med 1990; 19: 674–675.
48. Browne T. Paraldehyde, chlormethiazole, and lidocaine for treatment of status epilepticus. In: Delgado-Escueta A, et al (eds). Advances in neurology: status epilepticus, vol. 34. New York: Raven Press; 1983. p. 509–517.
49. Kofke W, Young R, Davis P, et al. Isoflurane for refractory status epilepticus: A clinical series. Anesthesiology 1989; 71:653–659.
50. Berg A, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: A quantitative review. Neurology 1991; 41:965–972.
51. Hauser W, Rich S, Annegers J, Anderson E. Seizure recurrence after a first unprovoked seizure: An extended follow-up. Neurology 1990; 40:1163–1170.
52. Annegers J, Shirts S, Hauser W, Kurland L. Risk of recurrence after an initial unprovoked seizure. Epilepsia 1986; 27:43–50.
53. McMicken D, Freedland E. Alcohol-related seizures: Pathophysiology, differential diagnosis, evaluation, and treatment. Emerg Med Clin North Am 1994; 12:1057–1080.
54. Rathlev N, D'Onofrio G, Fish S, et al. The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. Ann Emerg Med 1994; 23:513–518.
55. Chance J. Emergency department treatment of alcohol withdrawal seizures with phenytoin. Ann Emerg Med 1991; 20:520–522.
56. Hauser W. Prevention of post-traumatic epilepsy. N Engl J Med 1990; 323:540–541.
57. Temkin N, Dikmen S, Wilensky A, et al. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med 1990; 323:497–502.
58. Stenklyft P, Carmona M. Febrile seizures. Emerg Med Clin North Am 1994; 12:989–1000.

59. American Academy of Pediatrics. Practice parameters: Febrile seizures. Pediatrics 1996; 97:769–775.
60. French J. The long-term therapeutic management of epilepsy. Ann Intern Med 1994; 120:411–422.
61. Brown T, Pincus J. Phenytoin (Dilantin) and other hydantoins. In: Brown T, Feldman R, (eds). Epilepsy. Boston: Little, Brown, and Co.; 1983. p. 175–189.
62. Apfelbaum J, Caravati E, Kerns W, et al. Cardiovascular effects of carbamazepine toxicity. Ann Emerg Med 1995; 25:631–635.
63. Hojer J, Malmlund H, Berg A. Clinical features in 28 consecutive cases of laboratory confirmed massive poisoning with carbamazepine alone. Clin Toxicol 1993; 31: 449–458.
64. Seymour JF. Carbamazepine overdose features of 33 cases. Drug Safety 1993; 8:81–88.
65. Spiller HA, Krenzelok EP, Cookson E. Carbamazepine overdose: A prospective study of serum levels and toxicity. Clin Toxicol 1990; 28:445–448.
66. Wyte CD, Berk WA. Severe oral phenytoin overdose does not cause cardiovascular morbidity. Ann Emerg Med 1991; 21:508–512.
67. Gellerman GL, Martinez C. Fatal ventricular fibrillation following intravenous sodium diphenylhydantoin therapy. JAMA 1967; 200:161–162.
68. Unger AH, Sklaroff HJ. Fatalities following intravenous use of sodium diphenylhydantoin for cardiac arrhythmias. JAMA 1967; 200:159–160.
69. Zoneraich S, Zoneraich O, Siegel J. Sudden death following intravenous sodium diphenylhydantoin. Am Heart J 1976; 91:375–377.
70. Dolgin JG, Nix DE, Sanchez J, et al. Pharmacokinetic simulation of the effect of multiple-dose activated charcoal in phenytoin poisoning: Report of two cases. DICP 1991; 25:646–649.
71. Rowden AM, Spoor JE, Bertino JS. The effect of activated charcoal on phenytoin pharmacokinetics. Ann Emerg Med 1990; 19:1144–1147.
72. Weichbrodt GD, Elliott DP. Treatment of phenytoin toxicity with repeated doses of activated charcoal. Ann Emerg Med 1987; 16:1387–1389.
73. Stremski E, Brady W, Prasad K, Hennes H. Pediatric carbamazepine intoxication. Ann Emerg Med 1995; 25: 624–630.
74. Neuvonen PJ, Elonen E. Effect of activated charcoal on absorption and elimination of phenobarbitone, carbamazepine, and phenylbutazone in man. Eur J Clin Pharmacol 1980; 17:51–57.
75. Farrar HC, Herold DA, Reed MD. Acute valproic acid intoxication: enhanced drug clearance with oral activated charcoal. Crit Care Med 1993; 21:299–301.
76. Zawada ET, Nappi J, Done G, et al. Advances in the hemodialysis management of phenobarbital overdose. South Med J 1983; 76:6–8.

Emergency Department Management of Acute Myocardial Infarction

Edward Mintz, M.D.

Abstract

Myocardial infarction remains one of the leading causes of death among adults in the United States despite the significant advances in therapy made during the past three decades. However, a significant reduction in mortality following acute myocardial infarction has been accomplished through an aggressive strategy directed toward early recognition and intervention. This approach requires that the emergency physician act promptly and choose appropriately from the ever-expanding therapeutic options. This paper summarizes the recent progress and treatment options in the management of acute myocardial infarction with regard to prehospital care, diagnostic challenges in the emergency department, conventional therapy and pharmacologic advances, newer interventional measures, and future trends. **Key Words:** Myocardial infarction, emergency medicine, thrombolysis, streptokinase, tissue plasminogen activator, angioplasty, heparin, hirudin.

Each year in the United States approximately 1.5 million people have myocardial infarctions and nearly 500,000 of them die. Nearly 300,000 of these deaths occur before admission to the hospital, most of these within the first hours after symptoms begin (1). Coronary heart disease continues to be the leading cause of death among adults in the United States despite a remarkable 54% decline in age-adjusted mortality from 1963 to 1990 (2). In recent years, efforts have been directed toward both the earlier identification of acute myocardial infarction (AMI) and more rapid and effective treatment. Recent advances in thrombolytic therapy combined with the proper use of more "conventional" agents such as aspirin, nitroglycerin, and heparin have enabled the emergency physician to more effectively treat a heart attack and minimize its long-term sequelae.

Early Recognition and Initiation of Therapy

Early recognition and intervention have become crucial given the demonstrated benefit of thrombolytic therapy. The total delay time can be divided into phases: patient delay (the time it takes the patient to decide to seek medical attention); transportation delay (the time spent for transport to the hospital); and hospital delay (the time spent in the emergency department performing procedures and awaiting definitive evaluation) (3).

Minimizing Delays in Obtaining Care

Patient delay varies considerably among individuals, representing on average 50 to 65% of the overall time between onset of symptoms and delivery of definitive therapy (4). This delay is influenced by social and cultural factors, effectiveness of transportation, and severity of pain. It has been shown that patients with larger infarcts are more likely to make their decisions faster (5). Nonetheless, it is discouraging that despite a demonstrable benefit from early intervention, approximately 50% of patients with an AMI wait

---

From the Department of Emergency Medicine, Mount Sinai School of Medicine, Clinical Assistant Professor. Address correspondence to Edward Mintz, M.D., Box 1149, Mount Sinai School of Medicine, Department of Emergency Medicine, One East 100th Street, New York, NY 10029.

more than 4 hours before seeking medical attention. In addition, there is little evidence that public education programs have thus far been successful in reducing patient delay (6). Accordingly, it is imperative that patients with known coronary artery disease, or those with coronary risk factors (i.e., hypertension and diabetes) be educated concerning their response when symptoms of myocardial ischemia and infarction occur.

Perhaps the most troubling component of delay time is the "door-to-drug" time, the time between the AMI patient's arrival in the emergency department and initiation of thrombolytic therapy. An analysis of data from 51 patients treated at one hospital participating in the TIMI (Thrombolysis in Myocardial Infarction) II trial revealed an average of 89.9 minutes before tissue plasminogen activator (TPA) infusion was begun (7). Similar studies have identified "door-to-drug" times of 46 (8) and 70 (9) minutes; the largest components of these delays are the time between compiling data and formulating a treatment decision (20 and 22 minutes, respectively) and the time between deciding to administer and actually giving thrombolytic therapy (20 and 37 minutes, respectively). Much attention has been given to the development of protocols for identifying and rapidly assessing patients with suspected AMI. Regardless of which algorithm is used, it is increasingly clear that patients presenting to the emergency department with chest pain or chest-pain equivalent syndromes consistent with AMI should be given a priority evaluation to determine suitability for thrombolytic therapy, and once identified should be managed aggressively (10, 11). The decisions regarding suitability as well as authority to administer thrombolytic therapy is best left in the hands of the emergency physician (12). Other measures which should improve door-to-drug time include storage of drugs in the emergency department, employing ancillary staff dedicated to obtaining electrocardiograms, and quicker evaluation by the physician. Additionally, administration of aspirin, heparin, beta blockers, or nitrates should be initiated, if not contraindicated, while the decision about thrombolysis is being considered (2). Such measures, in coordination with ongoing quality assurance monitoring, have been demonstrated to achieve median arrival-to-treatment times as low as 17 minutes (13), well below the American Heart Association guideline of 30 to 60 minutes (14).

Prehospital Management

There is a growing body of evidence that early cardiopulmonary resuscitation (CPR) and prompt defibrillation have contributed significantly to overall survival in AMI. Witnessed ventricular fibrillation treated with almost immediate defibrillation will likely lead to survival and complete recovery (15). Accordingly, the American Heart Association has recommended that every ambulance expected to transport victims of cardiac arrest be equipped with a defibrillator. The initiation of thrombolytic therapy in the prehospital setting is more controversial. To the extent that prehospital-initiated thrombolytic therapy reduces the time to treatment there is a proven benefit in myocardial salvage (16). However, in a large multicenter trial involving 5,469 patients, a reduction in mortality from cardiac causes was seen without a clearly demonstrated reduction in overall mortality (17). Smaller studies have borne out similar results and conclusions, and have questioned the allocation of substantial financial and human resources for a yet unproven benefit (18). At present, although a reduction in presentation-to-treatment time is of paramount importance, it does not seem certain that prehospital thrombolysis is of any measurable benefit.

Diagnosis

The electrocardiogram (ECG) and history of chest pain or anginal equivalents remain the primary resources for screening patients for myocardial infarction and ischemia. A targeted history and physical examination should be performed promptly to assess the likelihood that the patient is presenting with an acute infarction, and to discriminate myocardial ischemia and infarction from conditions which might seem quite similar, such as pulmonary embolus, aortic dissection, pericarditis, and pneumothorax. However, the history may be somewhat nonspecific and the ECG might not yield a definitive diagnosis, especially if prior ECGs are not available for comparison. Moreover, the presence of a left bundle-branch block may mask electrocardiographic evidence of infarction (19).

Measurement of certain serum proteins may provide more precise information, but these studies often can not be obtained in a timely fashion before administration of thrombolytic therapy. An elevation in the MB isoenzyme of creatinine kinase (CK-MB) may not be seen for 3 to 8 hours after AMI and may not peak until 10 to 24 hours after the event (20). Elevations in lactate dehydrogenase (LD) and aspartate aminotransferase (AST) may not be seen for considerably longer, may be falsely elevated, and may be too nonspecific to be of value (21). In recent years, much attention has been given to the development of diagnostic markers possessing sufficient specificity and sensitivity and appearing early enough in the course of myocardial infarction to be of clinical utility. The cardiac forms of troponin T and I have been proposed to meet this challenge. However, the sensitivity and specificity of these proteins may not be considerably better than the measurements of CK-MB; and they appear in serum only slightly earlier than CK-MB (22). Elevations in serum myoglobin can be detected as soon as 1 hour after infarction (23). However, confounding variables including trauma, hypoxia, hypothermia, renal disease, and alcohol abuse may produce dramatic elevations in serum myoglobin concentrations rendering this marker nonspecific (21). A recently described subform of CK-MB has been developed which has a superior sensitivity and specificity. However, in one study sensitivity was only 56% at 4 hours after the onset of symptoms and improved to 96% at 6 hours (24).

The diagnostic utility of any of these markers depends on the time elapsed since the onset of symptoms and may be more useful in following trends as opposed to the absolute values at any given time. As such, the laboratory has limited utility and should not be relied on to guide the physician considering thrombolytic therapy. In cases where the history and ECG may be inconclusive, echocardiography might serve as a useful adjunct. Although not sensitive or specific enough when used alone to diagnose AMI, bedside two-dimensional transthoracic echocardiography may help distinguish an acute infarction from numerous other and potentially severe causes of chest pain. It should be considered in those cases where additional data are required (25).

Treatment in the Emergency Department

Routine Measures

Long before a decision is made to administer thrombolytic therapy or to seek invasive interventional measures, the initial evaluation and management of the patient with an AMI should include routine supportive measures. While obtaining the initial history and physical examination, care should be directed toward securing intravenous access, establishing cardiac monitoring in an appropriately supervised setting, relieving pain, and assuring hemodynamic and electrical stability (26). Once this is done the administration of oxygen, aspirin, and nitroglycerin should be considered.

Oxygen. Oxygen inhalation after acute coronary occlusion decreases the extent of ischemic injury, reduces the eventual extent of myocardial necrosis, and reduces ST-segment elevation (27, 28). Proposed mechanisms for oxygen's effectiveness include a reduction in myocardial tonic contraction in the ischemic regions after coronary artery occlusion, leading to a reduction in myocardial oxygen consumption and demand and correction of ventilation-perfusion mismatching, leading to mild hypoxemia (29, 30).

It is generally recommended, and has become standard practice, that oxygen should be administered to all patients suspected of having acute ischemic pain, at least during the first few hours after symptoms begin. In those patients for which AMI is complicated by severe congestive heart failure or pulmonary edema, mechanical ventilation is often required and should not be delayed.

Aspirin. The benefits of aspirin and the importance of its administration in AMI cannot be overemphasized. Aspirin, in single oral doses as low as 5–100 mg, exerts a dramatic and irreversible antiplatelet effect through the inhibition of platelet cyclooxygenase activity leading to the suppression of thromboxane A2 synthesis. Because affected platelets cannot be repaired during their lifetime, the duration of aspirin's effect is related to platelet turnover, explaining why a drug with a 20-minute half-life in the systemic circulation can be effective as an antiplatelet agent when administered only once a day (31).

The Second International Study of Infarct Survival (ISIS-2), a multicentered trial involving 17,187 patients in 417 hospitals, demonstrated the efficacy of aspirin in reducing mortality after AMI. A 23% reduction in 35-day mortality was demonstrated from aspirin alone. This figure was similar to that obtained using thrombolytic streptokinase, and underscores the effectiveness of aspirin therapy in AMI. When combined with streptokinase the reduction in mortality was 42% (32). Aspirin has also been demonstrated to be beneficial in the management of angina pectoris, in the prevention of recurrent myocardial infarction (33, 34), and recurrent ischemia and coronary reocclusion after thrombolysis (35).

The benefits and risks of aspirin are well established. Aspirin produces dose-dependent upper gastrointestinal complications, including nausea, vomiting, bleeding, and in severe cases, hemorrhage. With very high doses, an abnormal acid-base status may be observed; and with prolonged usage, renal impairment can result. However, it is unlikely that significant morbidity will result from the administration of a single oral dose in the 160- to 325-mg range (31). Thus, in the absence of active peptic ulcer disease or a history of hypersensitivity to salicylate, it seems prudent to administer a single oral dose of 160–325 mg of aspirin as soon as the diagnosis of AMI is entertained (32, 36).

Nitroglycerin. It is well established that nitroglycerin, by lowering myocardial oxygen demand and improving left ventricular compliance abnormalities, alleviates ischemic myocardial pain (37). However, nitroglycerin's effect in reducing infarct size and overall mortality is subject to ongoing debate (12, 38, 39). There are also studies demonstrating an effect by nitroglycerin in decreasing susceptibility to ventricular fibrillation (40). However, there is no conclusive evidence that the use of nitroglycerin decreases overall mortality in patients with an AMI.

In most patients sustaining an AMI, the use of nitroglycerin seems appropriate, especially in settings complicated by congestive heart failure or pulmonary edema. Administration can initially be sublingual. However, intravenous administration provides for more precise titration and can be terminated rapidly if hypotension ensues. Long-acting oral nitrate preparations should be avoided in the setting of AMI (12). There are, however, scenarios in which nitroglycerin must be given with extreme caution or avoided completely, because its administration may complicate or cause hypotension and bradycardia. For example, in patients presenting with an inferior wall myocardial infarction, right ventricular infarction must be suspected. This presents electrocardiographically with ST-segment elevation in the right precordial leads and may have an associated high-degree atrioventricular block. Clinical signs may include Kussmaul's sign (jugular venous distention during inspiration accompanied by clear lung fields) and hypotension. Echocardiography might be an especially useful tool in this setting. In the presence of right ventricular infarction, nitrate administration may further diminish an already impaired preload and result in profound hypotension, and as such, is contraindicated. The mainstay of therapy in right ventricular infarction remains volume loading and inotropic support with agents such as dobutamine (41). Bradycardia is a less frequent complication of nitroglycerin administration and is thought to represent a failure of normal compensation by the baroreceptor mechanisms. This may occur in a setting of enhanced vagal tone and diminished sympathetic activity (42).

Analgesia. The complete relief of pain accompanying reperfusion after administration of thrombolytic therapy suggests that pain is a marker for ongoing ischemia. Measures that are directed at reducing ischemia will likely reduce pain as well (43). Pain relief in and of itself may reduce myocardial oxygen demand and reduce the likelihood of arrhythmia (44).

Morphine sulfate appears to be the agent of choice if anti-ischemic therapy alone fails to alleviate pain. Morphine administration causes peripheral venous and arterial dilation, leading to a reduction in preload and afterload and a resultant decrease in myocardial oxygen demand (45). However, administration of narcotics may produce hypotension and respiratory depression. Dosing must be carefully individualized in an appropriately monitored setting.

Thrombolysis

One of the most significant advances contributing to the significant reduction in mortality from myocardial infarction has been the development of fibrinolytic therapy. Composite data from nine trials involving 58,600 patients demonstrated an 18% reduction in 35-day mortality from thrombolysis versus control. However, the thrombolytic agents are not benign drugs, causing stroke and major noncerebral bleeds at average excess rates of 3.9 per 1,000 and 7.3 per 1,000, respectively (46). Moreover, the benefits of thrombolysis appear to diminish as more time elapses after the onset of chest pain. As discussed above, a rapid and targeted evaluation must be performed on all patients presenting to the emergency department with suspected myocardial infarction to offer thrombolytic therapy to those meeting appropriate inclusion criteria.

Selection of Patients. The initial clinical trials for thrombolytic therapy were generally directed toward younger patients who presented within the first few hours of symptoms and who did not have significant comorbidities. It was thought that these patients would benefit most from thrombolytic therapy. However, with time, more elderly patients and those with concomitant medical problems also derived significant benefit from administration of thrombolytic therapy and inclusion criteria were gradually broadened (47). An age greater than 75 years was initially a reason for exclusion, because of an increased risk of serious bleeding consequences and stroke (48, 49). The fragile nature of elderly patients predisposes them to an increased risk of complications as well as statistical benefit from administration of thrombolytic therapy. The elderly patient is less likely to survive an AMI without thrombolytic therapy. It is in this elderly cohort that the highest percentage increase in overall survival due to administration of thrombolytic therapy is seen. Recent trials support the contention that thrombolytic therapy is an appropriate and cost-effective treatment for AMI in all age groups. Nonetheless, substantial differences persist in the proportions of older and younger patients receiving thrombolytics (50, 51). On what basis then is thrombolytic therapy appropriate and when should it be excluded?

The time from the onset of symptoms to treatment is clearly an important factor. Although the benefits of thrombolysis seem to be greatest when administered during the first 6 hours after infarction, more recent data demonstrate a worthwhile benefit for TPA administration given up to 12 hours after infarction (52, 53). Benefits have also been seen for streptokinase administration in the 6- to 24-hour time frame. However, with the passage of time, the beneficial effect of thrombolytic therapy seems to lessen. Eventually, a point in time is reached at which the risk of administration of thrombolytic therapy outweighs the probability of benefit and does not seem justified (32, 54). Electrocardiographic inclusion criteria are also in a state of evolution. The benefit of thrombolysis has been well established in myocardial infarction presenting with ST-segment elevation in two or more contiguous leads. However, there is an increasing awareness that patients who have unstable chest pain presenting with a new left-bundle branch block may also benefit (55). Administration of thrombolytic therapy in cases where an equivocal ECG may represent unstable angina or a non-Q-wave myocardial infarction or nonischemic sources of chest pain (e.g., pericarditis or aortic dissection), however, is probably not beneficial and may be harmful (56, 57). Although a history of chest pain characteristic of infarction and persisting for longer than 30 minutes may be present, the nature and quality of chest pain may be misleading. Furthermore, rigid application of inclusion criteria may exclude many patients sustaining an AMI for whom thrombolytic therapy would be beneficial and appropriate (58).

There are situations in which thrombolysis should we withheld, however. As the principal risks from administration of thrombolytic therapy are related to bleeding complications, it would seem wise to exclude patients for the following reasons: major surgery or trauma within the previous 6 weeks; recent head trauma; known intracranial tumor or any previous neurosurgery; a history of stroke or active peptic ulcer disease within the past 6 months; and known or suspected aortic dissection or pericarditis. Other significant exclusion criteria which may be modified in accordance with the clinical scenario include prolonged cardiopulmonary resuscitation and acute severe hypertension. Factors which have been associated with a higher risk of bleeding complications, but do not preclude thrombolysis, include the presence of diabetic retinopathy, older age, a history of hypertension, female sex, and small body size (59–61).

Selection of Thrombolytic Agents. The selection of a thrombolytic agent is fraught with controversies regarding safety, efficacy, and cost. Three agents, streptokinase (SK), TPA, and anisoylated plasminogen-streptokinase activator complex (APSAC, antistreplase) have been studied extensively. SK and TPA are in widespread use in the United States; APSAC has been studied in Europe. Comparison among these agents has included the use of adjuncts including aspirin and heparin, has examined dosing variations in the amount and rapidity of administration (e.g., "front-loading"), and has compared and contrasted these agents in subgroup analysis by age, comorbidity, and time delay in presentation.

Some differences have been demonstrated and should be noted: ISIS-3 (The Third International Study of Infarct Survival Collaborative Group) randomized SK versus TPA versus APSAC among 41,299 cases of AMI. In this study all patients received aspirin. Approximately half received heparin in addition to fibrinolytic therapy. There was significantly more systemic bleeding as well as stroke from TPA versus SK but fewer reports of significant allergic reactions and of hypotension requiring pharmacologic intervention. Although fewer reinfarctions were seen with TPA, there were no significant differences in the 35-day mortality and 6-month survival between these two agents. Similarly, when APSAC was compared with SK, APSAC administration led to more reports of allergy causing persistent symptoms, more noncerebral bleeds, an excess of strokes but no significant differences in the reinfarction rate, 35-day mortality, and 6-month survival rates. These differences were noted independent of heparin administration (62).

The GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial, involving 41,021 patients in 1081 hospitals in 15 countries also examined TPA versus streptokinase. However, the TPA was "accelerated." ("Accelerated" TPA is TPA given over 1½ hours, with two thirds of the dose given in the first half hour versus conventional TPA administration given as a steady-state infusion over 3 hours.) GUSTO patients were randomly selected for four different thrombolytic regimens: SK + subcutaneous (SC) heparin; SK + intravenous (IV) heparin; "accelerated" TPA + IV heparin; or a combination of SK + TPA + IV heparin. GUSTO demonstrated a significantly higher rate of stroke in the TPA group as compared with both SK-alone groups. However, this was more than offset by an overall reduction in mortality in the TPA group. Using a combined end-point of death or disabling stroke the rate was 6.9% in the TPA group versus 7.8% in the SK-only groups (63).

Despite the superiority of accelerated TPA to SK in the GUSTO trial, cost and ease of administration have become prominent considerations in the challenging arena of managed care. Accelerated TPA must be accompanied by intravenous heparin, the administration of both costing $2,300, as compared with streptokinase (without heparin) which costs $320 (63, 64). Another concern is the substantial risk of anaphylaxis from a second exposure to SK or APSAC. As such, these agents are contraindicated in patients who have received them in prior thrombolytic therapy (12). For these patients, TPA is the thrombolytic agent of choice. Regardless of which agent is used, thrombolytic therapy is a proven life-saving therapy in AMI, yet it is still often not administered as quickly and efficiently as it should be (47).

Angioplasty

The first percutaneous transluminal coronary angioplasty (PTCA) was performed in 1977 (65). Although its applications initially were limited to the treatment of discrete stenoses in the proximal segment of a coronary artery as a less invasive measure than coronary artery bypass grafting (CABG) for the treatment angina, PTCA has been studied extensively in the management of AMI. In conjunction with administration of thrombolytic therapy, immediate angioplasty after successful thrombolysis has not been found to provide any benefit over delayed angioplasty (66). Prophylactic PTCA after successful thrombolysis was found to not only provide no additional benefit but could actually contribute to mortality in those patients prone to hemorrhage (67). However, in trials evaluating primary ("direct") angioplasty in place of thrombolytic therapy, subgroups of patients with higher risks for hemorrhage (e.g., uncontrolled hypertension, recent major surgery, cerebrovascular accident, prolonged CPR) and those in cardiogenic shock, fared better with PTCA (68, 69). In patients with single-vessel disease, a 50% improvement in global ejection fraction and improved long-term survival has been demonstrated after direct angioplasty (70). In the PAMI (Primary Angioplasty in Myocardial Infarction) study comparing direct PTCA and thrombolysis, the in-hospital mortality was 6.5% for the TPA-treated group versus 2.6% for patients receiving primary PTCA. Reinfarction and death rates were also significantly higher at 6 months for the TPA-receiving cohort (71). Strategies which use angioplasty for unsuccessful thrombolysis ("rescue" angioplasty) when used judiciously in high-risk patients have also shown promising results (72). Primary PTCA should be considered if a patient presents to a center that has expertise in PTCA if the patient has high risk (e.g., with a large anterior wall MI or in cardiogenic shock) or has a contraindication to thrombolytic therapy.

Adjuncts to Thrombolysis Or Angioplasty

As discussed previously, oxygen, aspirin, nitrates, and analgesia, and possibly thrombolytics, are the mainstay of pharmacologic management of AMI, irrespective of other strategies. A host of other drugs may serve as useful adjuncts in the acute setting. Others, however, have been met with mixed success.

Beta Blockers. One of the first large trials evaluating the use of β-blocker agents was the Metoprolol In Acute Myocardial Infarction (MIAMI) study published in 1985. Modeled after several smaller studies, the MIAMI group evaluated data on 26,439 patients, excluded 20,661 (approximately half due to current use of β-blockers or calcium channel blockers) for an ultimate enrollment of 5,778 patients. Approximately equal numbers were then assigned to placebo or control. Those receiving metoprolol were given three 5-mg-IV boluses at 2-minute intervals. In this group, there was a 13% overall reduction in mortality (29% in the high-risk group [defined as having ⩾3 cardiac risk factors]) after 15 days; a reduction in the serum aspartate aminotransferase after 3 days; and a reduction in the use of narcotic analgesics and other antianginal drugs. Moreover, metoprolol was generally not associated with significant hemodynamic embarrassment and did not seem to be detrimental to many patients (73).

The First International Study of Infarct Survival Collaborative Group (ISIS-1) evaluated the use of atenolol in 16,027 patients. This multicenter trial demonstrated a 15% reduction in vascular mortality during the first week, and 9% at 1 year, when atenolol was administered in the peri-MI period. Summary data from 28 randomized trials presented in ISIS-1 link administration of atenolol to a 14% reduction in deaths within the first 7 days; and 18% reduction in reinfarction rates; and a 15% reduction in cardiac arrest or ventricular fibrillation (74).

More recent studies and subgroup analyses continue to demonstrate a reduction in peri-MI mortality from β-blocker administration. However, the long-term benefits of continued administration are best seen in the higher risk patients. β-blockers are well tolerated by most patients. Therefore, it seems prudent to consider β-blockade in the initial treatment regimen in the emergency department (36, 75).

Heparin. The anticoagulant effect of heparin depends on its binding to a plasma cofactor named antithrombin III (ATIII) (76). The heparin/ATIII complex catalyzes the inactivation of factors IIa (thrombin), Xa, IXa, Xa, XIa, and XIIa. Heparin also binds to platelets, inhibiting platelet function and contributing to its hemorrhagic effects (77).

When compared with untreated controls, the use of heparin has been demonstrated to result in a 61% reduction in reinfarction when administered subcutaneously to patients who had a myocardial infarction 6 to 18 months before enrollment (78), and a 44% reduction in mortality in patients sustaining an AMI (79). However, with the more recent widespread use of thrombolytics and aspirin the added benefit from heparin is not as clear-cut. Early trials favorably comparing heparin versus aspirin (ASA) in maintaining vessel patency after thrombolysis have been criticized for using an inadequate dose of aspirin (77). Subsequent studies have examined the addition of heparin to regimens already including aspirin. Col et al. (80) did not find any significant increase in vessel patency at 24 hours in the heparin + SK + ASA group as compared with the SK + ASA only group (80). In the Duke University Clinical Cardiology Studies investigators randomly selected patients receiving APSAC + ASA for heparin or control. There too, no significant difference in coronary artery patency was seen in the heparin-treated group (81). ISIS-3 (62), GUSTO 1 (63), and GISSI-2 (82) were large multicentered trials assessing differences in thrombolytic agents and heparin. In all three trials, there was not sufficient evidence, using mortality rates as end points, to support the routine use of heparin with ASA and SK or APSAC. In fact, in ISIS-3 there was a significant excess rate of hemorrhagic stroke.

There does seem to be a benefit from heparin when TPA is chosen as the thrombolytic agent. In the GUSTO trial, TPA given with heparin produced significantly higher rates of infarct-related artery patency at 90 minutes as compared with SK + heparin (81% versus 60%), suggesting the superiority of TPA in establishing rapid reperfusion (83). However, it is the administration of heparin, not TPA, that appears to be responsible for maintenance of vessel patency in the TPA-treated group. In a smaller study of 84 patients treated with TPA, vessel patency at 48 to 72 hours after the initiation of therapy was 71% in the heparin-receiving cohort versus 43% for the controls (84). TPA is more fibrin-specific and has a shorter half-life than SK or APSAC. These differences may be responsible for maintaining long-term vessel patency in TPA-treated patients receiving heparin.

Heparin may also have additional benefit in a large anterior wall infarction in which left ventricular thrombus may occur. These thrombi are thought to significantly increase the risk of embolic stroke. There is some evidence that a reduction in this risk can be attained through the administration of intravenous heparin early in the course of infarction (32, 85).

Overall, the routine use of heparin in myocardial infarction may not be warranted. The added benefit of heparin given with less specific fibrinolytic agents is not supported, and may result in an increased risk of bleeding (62, 82, 86) and thrombocytopenia, the latter more recently associated with prothrombotic events (87). However, if TPA is used as a thrombolytic agent, then the administration of heparin early in the course of treatment appears essential (88). Similarly, in situations where the risk of embolic phenomena appears high, the use of heparin may justify the risks.

Hirudin. Hirudin has been in clinical use for centuries. It is a potent, direct, highly specific inhibitor of both free clot and unbound thrombin found in the saliva of the medicinal leech, *Hirudo medicinalis* (89). Through recombinant technology, desulfatohirudin (hereinafter referred to as hirudin) is available as an intravenous preparation.

Several studies have been conducted in the past few years to evaluate hirudin as an adjunct to thrombolysis and as an alternative to heparin; they have had very promising results. In the TIMI 5 trial, AMI patients were treated with front-loaded TPA and ASA and were randomized to hirudin (in four different doses) or heparin. Overall, the hirudin-treated patients had superior TIMI grade 3 flow in the infarct-related artery at 90 minutes (64.8% versus 57.1%); superior patency (TIMI grade 2 or 3 flow) at 18 to 36 hours (97.8% versus 89.2%); a reduced rate of reocclusion at 18 to 36 hours (1.6% versus 6.7%); a reduced rate of death or reinfarction during the hospital period (6.8% versus 16.7%); and a lower rate of major spontaneous hemorrhage (1.2% versus 4.7%) (90). TIMI 6 had similar conclusions, with the added caveat that higher doses of hirudin are associated with a lower rate of mortality and reinfarction than the lower doses, although this lacked sufficient statistical power to be conclusive (89).

The dosing of hirudin, and for that matter heparin, is not yet well established and remains under evaluation. The TIMI 9A trial, comparing the safety and efficacy of intravenous hirudin vs. aspirin, was terminated early because of an excess of hemorrhagic stroke. Drawing from evidence in the GUSTO trials (63, 83), higher doses of heparin and hirudin, resulting in higher activated partial thromboplastin times (aPTT), were associated with excess bleeding complications (91). Larger trials are needed to confirm hirudin's promising potential in the management of unstable angina (92).

Calcium Channel Blockers. Numerous trials have failed to demonstrate a beneficial effect from immediate-release preparations of nifedipine and verapamil in the management of AMI. The use of such preparations has proven harmful, having been associated with excess mortality in some of these studies (93–96). Diltiazem, however, in a long-acting preparation seems to be better tolerated and may prevent early reinfarction after a non-Q-wave AMI in patients with good left ventricular function, but it may be deleterious in larger infarctions or patients with left ventricular dysfunction (97, 98).

Although the widespread use of calcium channel blockers appears contraindicated, these agents may be quite beneficial in certain circumstances. Calcium channel blockers have been shown to inhibit vasoconstriction of vascular smooth muscle (99). As such they may be beneficial in vasospastic angina and perhaps in cocaine-induced myocardial infarctions which have been demonstrated angiographically in patients with normal coronary arteries and at autopsy (100).

Angiotensin-Converting Enzyme Inhibitors. After AMI, ventricular remodeling and dilation can occur leading to an increased risk of heart failure, arrhythmia, and death. Also, activation of the renin-angiotensin system may increase the heart rate and systemic vascular resistance, decrease coronary artery perfusion, all resulting in infarct expansion. Angiotensin-converting enzyme (ACE) inhibitors have been beneficial in diminishing the harmful physiological sequelae of AMI and are frequently administered to the post-MI patient (101). However, there are conflicting data regarding exactly how early in the course of infarction ACE inhibitor therapy should be initiated.

In the CONSENSUS-II trial patients were randomly selected within the first day to receive either intravenous enalaprilat or placebo, followed by oral doses of either. Severe hypotension developed in about 10% of the patients randomly selected to receive enalaprilat; an occurrence approximately 2½ times more frequent than found in the placebo group. This trial was prematurely terminated because of the higher complication rate demonstrated in the enalaprilat-treated cohort (102). The ISIS-4 study, however, demonstrated a beneficial effect from the early use of ACE inhibitors. In ISIS-4, approximately half of the 58,050 patients were randomly selected to receive either oral captopril or placebo begun within 24 hours of a suspected AMI. The captopril-treated patients had a 7% proportional reduction in 5-week mortality. There was also a modest reduction in 1-year mortality, and surprisingly, in deaths occurring in the first day of treatment. There was a slight excess of cardiogenic shock and severe hypotension in the captopril-treated patients, but these complications seemed offset by the overall mortality statistics. Study patients were also randomly selected to receive oral mononitrate versus placebo and intravenous magnesium sulfate versus placebo. However, controlling for these additional variables, there was still an excess of five lives saved per 1000 treated with captopril at 1 month (103).

From these studies, and similar small trials, it seems that intravenous enalaprilat should be avoided in the acute phase of infarction. However, the administration of oral ACE inhibitors early in the course of infarction may be quite useful in reducing mortality and preventing complications in large anterior wall infarction. In non-Q-wave infarction, the subgroup analysis from the CONSENSUS-II, GISSI-3, and ISIS-4 trials is not as convincing (102–104). In all cases, administration of these agents probably should await stabilization of blood pressure, should be given in gradually increasing dosage, and may need to be terminated if hemodynamic embarrassment results.

Magnesium. Magnesium has inhibited platelet function, produced coronary vasodilation, and protected myocytes against calcium overload in ischemic states (105, 106). Magnesium deficiency has been associated with a variety of cardiovascular disease states (107). As such, numerous trials have been conducted to establish a role for magnesium in the management of AMI. In the LIMIT-2 trial, from 1987 to 1992, 2,316 patients were randomly selected in a double-blinded fashion to receive either intravenous magnesium sulfate (given as an 8 mmol [approximately 1 g] bolus followed by a 65-mmol [approximately 7.8 g] infusion over 24 hours) or intravenous saline. At the 28-day end point, the overall mortality was 10.3% in the placebo group and 7.8% in the magnesium-receiving cohort (108). This mortality reduction was seen for at least 4 years in these patients' follow-up studies (109). However, in the larger ISIS-4 study, of similar design with respect to magnesium dosing and route of administration, there was no significant reduction in mortality in the magnesium-treated cohort (103).

Woods and Fletcher (109), two of the LIMIT-2 investigators, suggest that the timing of magnesium administration, which differed in these studies, may account for the conflicting results. In ISIS-4, the time from onset of symptoms to randomization was considerably longer (8 versus 3 hours). Also, in ISIS-4, magnesium therapy was deferred until after administration of thrombolytic therapy was complete (109). Subgroup analysis from both studies indicated that patients receiving magnesium earlier in the course of infarction derived a greater benefit.

From these studies, it would seem that if magnesium is to be given in the treatment of AMI it should be given early. Although there may be an overall reduction in mortality with magnesium administration as compared with placebo, subgroup analysis has not convincingly demonstrated a significant additional benefit when aspirin and thrombolytic therapy are administered. Magnesium may be useful in candidates thought not suitable for thrombolysis (110) and in the treatment of torsade de pointes (111).

Management of Complications

In managing AMI, the emergency physician is confronted not only with diagnostic and therapeutic challenges, but also with complications of infarction which may be evident upon presentation or may develop early in the course of treatment. Potential complications are too numerous to discuss fully in a brief review. However, certain conditions occurring more frequently and with potentially more devastating consequences, if not managed promptly and properly, are discussed below.

Cardiogenic Shock

Pump failure must be suspected in patients with an AMI who have cool or cyanotic extremities, hypotension, weak pulses, oliguria, and who are obtunded. These patients may have varying degrees of pulmonary congestion. Moreover, cardiogenic shock is typically an evolving process which, if not reversed, has a mortality rate of 50% to 80% (26). Once other causes of shock, such as aortic dissection, pulmonary embolism, and sepsis, are excluded, management should be directed toward correcting the hemodynamic derangement. Diuresis with furosemide may alleviate the pulmonary congestion. Reduction of afterload can be accomplished by administration of nitroglycerin. However, both of these interventions may be contraindicated by a low arterial blood pressure, which may drop even further from therapy.

One might consider use of an intra-aortic balloon pump (IABP) to improve hemodynamic function in myocardial infarction complicated by cardiogenic shock. IABP counterpulsation serves several ends: augmentation of effective hemodynamic flow, relief of chest pain, and possibly prevention of infarct expansion in jeopardized myocardium (112, 113). Moreover, the IABP may serve as an adjunct to reperfusion therapy in treating patients at high risk for reocclusion after thrombolytic therapy and PTCA (114, 115). Although insertion of an IABP is associated with vascular complications, including dissection, and significant bleeding in the post-thrombolytic state, the potential benefit of therapy may significantly outweigh the calculated risks (14).

Primary angioplasty is an important consideration in reducing mortality in AMI complicated by cardiogenic shock. In one retrospective uncontrolled study, *successful* primary angioplasty was reported to have reduced 30-day mortality in patients sustaining an AMI complicated by shock to 23% as compared with 84% in those treated with conventional therapy which did not include administration of thrombolytic therapy (116). *Unsuccessful* emergent PTCA, however, has no added benefit on survival and may actually increase mortality in these patients (117). Interestingly enough, thrombolytic therapy has not been shown to produce any significant increase in survival in patients in cardiogenic shock (10).

Ventricular Arrhythmia

Ventricular Fibrillation. Primary ventricular fibrillation (VF) occurs at an incidence of about 3% to 5% in the first 4 hours after an AMI. Secondary VF occurs in the later stages of a myocardial infarction, typically as a consequence of cardiogenic shock and/or congestive heart failure (118, 119). Although the incidence of primary VF has diminished with the use of β-blockers and correction of electrolyte deficiencies, the development of VF is rapidly fatal (120). VF should be treated with rapid nonsynchronized direct current of at least 200 to 300 joules, initially followed by adjunctive pharmacologic therapy including epinephrine, lidocaine, and/or bretylium, all in concert with repeated defibrillatory shocks until termination of the arrhythmia is achieved (26). Intravenous amiodarone has recently been approved by the Food and Drug Administration as an additional pharmacological intervention in refractory cases.

Ventricular Tachycardia. Short bursts of ventricular tachycardia (VT) occur frequently in the acute phase of a myocardial infarction and do not necessarily require intervention. Episodes which are sustained (usually defined as 30 seconds or longer) or accompanied by hemodynamic compromise must be treated (121). Rapid polymorphic VT should be managed as VF and be treated with unsynchronized defibrillation.

Prophylactic therapy with lidocaine was once popular. However, results from randomized trials have demonstrated an increased mortality from routine use of class I antiarrhythmic agents after AMI, and this practice has been largely discontinued (119, 120, 122).

Bradycardia and Heart Block

Sinus bradycardia is a frequent occurrence in the setting of AMI, especially within the first hour of an inferior wall myocardial infarction. Bradycardia may also occur as a consequence of reperfusion of the right coronary artery (Bezold-Jarish reflex) (123). Heart block may develop in about 20% of patients with an inferior wall MI, and is associated with a higher in-hospital mortality (124, 125).

Symptomatic sinus bradycardia usually can be treated effectively with atropine which enhances sinus node automaticity and atrioventricular conduction via direct vagolytic action (126). Atropine may also be useful for correcting the sinus bradycardia and hypotension associated with thrombolytic therapy (127). However, atropine should be administered with caution. In the setting of AMI, parasympathetic tone is thought to have a protective effect against VF and infarct extension (128). Atropine administration has been associated with VF and VT (129).

In the setting of AMI where the development of heart block is of concern, the emergency physician should have an external transcutaneous pacemaker at his disposal. This device can be left in the standby mode to correct heart block if it develops and to prevent the sequelae of bradyarrhythmias (130). If symptomatic heart block has developed, placement of a transvenous pacemaker should be considered. In a large series from the Mayo Clinic, use of a transvenous pacemaker was associated with a complication rate of 13.7%. However, none of these complications was associated with an excess in mortality (131). Although transvenous pacemaker insertion is more time consuming and involves the risks associated with achieving venous access and epicardial or myocardial injury, it offers the superiority of minimizing the discomfort induced by transcutaneous pacing.

Future Trends

Ongoing improvements in the management of AMI include the development of pharmacologic adjuncts to thrombolysis directed at accelerating clot lysis and preventing rethrombosis. To maximize the effectiveness of therapy, thrombolysis and interventional strategies must be used in the first few hours after a myocardial infarction. Toward that end, improvements in the speed at which an accurate diagnosis of AMI can be made are continually being sought.

Among the newer thrombolytic agents being evaluated is TPA TNK (Genetech), a variant of recombinant TPA. TPA TNK has an 8-fold higher thrombolytic activity than that of TPA and is proposed as a more efficacious agent (132). Reteplase or Mini TPA (Boerhinger Mannheim BM 06.022) has been given to patients with AMI as a single bolus resulting in more rapid thrombolysis than standard thrombolytic therapy. Encouraging results from both of these agents are been seen in ongoing trials (133, 134).

Also promising are new antiplatelet agents directed against the GPIIb/IIIa receptor. Monoclonal antibodies directed against the GPIIb/IIIa receptor have the advantage of being platelet specific and of leaving platelet adhesion functioning, which may contribute to hemostasis without producing vasoocclusion (135). Given in addition to aspirin and high-dose heparin, administration of a monoclonal antibody directed against platelet

GPIIb/IIIa receptors resulted in a 35% reduction in adverse events after PTCA. Adverse events were defined as death, myocardial infarction, or the need for an urgent intervention (repeat PTCA, coronary artery bypass surgery, stent placement, or IABP insertion) within the first 30 days as primary end points (136). The application of this antibody to the management of AMI is a fertile area for exploration. Also of interest is MK-383, a nonpeptidyl tyrosine derivative, which produces a dose-dependent inhibition of GPIIb/IIIa-mediated platelet aggregation. MK-383 is presently being evaluated for the prevention of acute closure after PTCA and for management of unstable angina (137).

Future trends also include a push toward a more rapid, accurate diagnosis of AMI. Algorithms which incorporate the use of bedside assays for the detection of myoglobin, troponin, and CK-MB are being used to more rapidly identify the presence of myocardial infarction minutes after a patient presents to the emergency department. Evaluation of panels of markers might be useful in those patients who present more than 1 to 2 hours after the onset of pain and are still within the thrombolytic "window" (138–140). Also, myocardial imaging studies using ultrafast computer tomography or magnetic resonance imaging may supplant the use of echocardiography in evaluating ventricular remodeling after infarction. These techniques may be able to identify "stunned" (reversible dysfunction after prolonged ischemia and reperfusion) and "hibernating" (reversible dysfunction resulting from chronic hypoperfusion or from repeated episodes of ischemia) myocardium. Identification of these viable zones has implications for revascularization strategies (141).

Conclusion

The past two decades have witnessed tremendous progress in the management of AMI and in reducing morbidity and mortality. The emergency physician now has a variety of diagnostic and therapeutic options available, and must intervene rapidly to provide proper medical care. The failure of the emergency physician to intervene rapidly is one of the leading causes of medical malpractice claims in emergency medicine today (142). Moreover, a decline in the incidence of myocardial infarction has also recently been seen and may be attributable to lifestyle modification including smoking cessation and diet modification (143). In an era of managed care and rationing of health care resources, the emergency physician has an increasingly challenging and complex role in the management of cardiovascular disease and AMI.

Acknowledgments

I am grateful to Dr. Howard Eisenstein, Dr. Sheldon Jacobson, and Dr. Andy Jagoda of the Department of Emergency Medicine at the Mount Sinai School of Medicine for their editorial assistance in the revision of this manuscript. I would also like to thank Shaindy Aber of the Mount Sinai School of Medicine for her assistance in compiling background materials.

Glossary of Acronyms for Selected AMI Trials

Acronym	Trial Name/Study Group	Description	Reference Citation[a]
CONSENSUS II	Cooperative New Scandinavian Enalapril Survival Study	Mortality study of early administration of enalapril vs placebo	N Engl J Med 1992; 327:678–684
DAVIT I and II	Danish Study on Verapamil in Myocardial Infarction	Mortality study of verapamil vs placebo post-MI	Eur Heart J 1984; 5:516–528
DUCCS	Duke University Clinical Cardiological Study	Comparison of intravenous heparin plus APSAC vs APSAC alone in maintaining vessel patency	J Am Coll Cardiol 23: 11–18
EMERAS	Estudio Multicentrico Estreptoquinasa Repulicas de America del Sur Collaborative Group	Mortality study of late (7–24 h after onset of AMI) treatment with SK vs placebo	Lancet 1993; 342:767–772
FTT	Fibrinolytic Therapy Trialists Collaborative Group	Collaborative overview mortality and morbidity results from several randomized trials	Lancet 1994; 343:311–322.
GISSI	Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico	Mortality study of SK vs placebo	Lancet 1986; 1:397–402.
GISSI-2	Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico	Mortality study of SK vs TPA and subcutaneous heparin vs no heparin	Lancet 1987; 2:871–874
GISSI-3	Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico	Mortality study of lisinopril vs nitrates vs both	Lancet 1994; 343:1115–1122
GUSTO	Global Utilization of Streptokinase and TPA in Occluded Coronary Arteries	Mortality study of TPA SK, intravenous and subcutaneous heparin in various combined regimens	N Engl J Med 1993; 329:673–682
INTERCEPT	Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Thrombolysis Research Group	Mortality study of long-acting diltiazem plus ASA vs ASA alone in patients receiving thrombolysis with a first AMI	Am J Cardiol 1995; 75:1120–1123

Acronym	Trial Name/Study Group	Description	Reference Citation[a]
ISIS-1	International Study of Infarct Survival Collaborative Group	Mortality study of of atenolol vs placebo	Lancet 1986; 2:57–66
ISIS-2	International Study of Infarct Survival Collaborative Group	Mortality study of SK, ASA, both, or neither	Lancet 1988; 2:349–360
ISIS-3	International Study of Infarct Survival Collaborative Group	Mortality study of SK vs TPA vs APSAC and of ASA plus heparin vs ASA alone	Lancet 1992; 339:753–770
ISIS-4	International Study of Infarct Survival Collaborative Group	Mortality study of oral captopril, oral mononitrate, and intravenous magnesium	Lancet 1995; 345:669–685
LATE	Late Assessment of Thrombolytic Efficacy	Mortality study of late (6–24 h after onset of AMI) administration of alteplase (TPA)	Lancet 1993; 342:759–766
LIMIT-2	Leicester Intravenous Magnesium Intervention Trial	Mortality study of intravenous magnesium vs placebo	Lancet 1992; 339:1553–1558
MIAMI	Metoprolol in AMI	Mortality study of metoprolol as adjunctive therapy	Am J Cardiol 1985; 56:1G–57G
MITI	The Myocardial Infarction Triage and Intervention Trial	Prehospital vs hospital-initiated thrombolytic therapy	J Am Coll Cardiol 1991; 18:657–662 JAMA 1993; 270:1211–1216
PAMI	Primary Angioplasty in Myocardial Infarction Study Group	Comparison of immediate angioplasty and thrombolytic therapy	N Eng. J Med 1993; 328:673–679
SCATI	Studio sulla Calciparina nell' Angina e nella Trombosi Ventricolare nell'Infarto Group	Comparison of subcutaneous heparin vs no heparin in patients treated and not treated with SK	Lancet 1989; 2:182–186
SPRINT	Secondary Prevention Reinfarction Israeli Nefedipine Trial	Mortality study of nifedipine vs placebo post-MI	Eur Heart J 1988; 9:354–364
SPRINT 2	Secondary Prevention Reinfarction Israeli Nefedipine Trial	Mortality study of nifedipine vs placebo post-MI	Arch Intern Med 1993; 153:345–353
TAMI	Thrombolysis and Angioplasty in Myocardial Infarction	Comparison of immediate vs delayed elective angioplasty after TPA	N Engl J Med 1987; 317:581–588
TAMI-3	Thrombolysis and Angioplasty in Myocardial Infarction	Comparison of TPA plus heparin vs TPA alone	Circulation 1989; 79:281–286
TAMI-5	Thrombolysis and Angioplasty in Myocardial Infarction	Comparison of combination thrombolytic therapy vs monotherapy and timing of cardiac catherization	Circulation 1991; 83:1543–1556
TAMI-7	Thrombolysis and Angioplasty in Myocardial Infarction	Comparison of five accelerated dosing regimens of TPA	J Am Coll Cardiol 1992; 19:482–489
TIMI II	Thrombolysis in Myocardial Ischemia	Comparison of invasive and conservative strategies after treatment with TPA	N Engl J Med 1989; 320:618–627
TIMI IIIB	Thrombolysis in Myocardial Ischemia	Comparison of early invasive and conservative strategies in unstable angina and non-Q-wave MI	Circulation 1994; 89:1545–1556
TIMI 4	Thrombolysis in Myocardial Ischemia	Comparison of front-loaded TPA, APSAC, and combination of both	J Am Coll Cardiol 1994; 24:1602–1610
TIMI 5	Thrombolysis in Myocardial Ischemia	Comparison of hirudin and heparin in patients receiving front-loaded TPA plus ASA	J Am Coll Cardiol 1994; 23:993–1003
TIMI 6	Thrombolysis in Myocardial Ischemia	Comparison of different dosages of hirudin and heparin	Am J Cardiol 1995; 75:7–13
TIMI 9A	Thrombolysis in Myocardial Ischemia	Comparison of efficacy and safety of hirudin vs heparin at different doses	Circulation 1994; 89:1557–1566

[a] Certain studies may have been published in several parts and/or in multiple journals. At least one relevant citation is provided.

References

1. Fuster V, Dyken ML, Vokonas PS, Hennekens C. Aspirin as a therapeutic agent in cardiovascular disease. Special Writing Group. Circulation 1993; 87:659–675.
2. National Heart Lung and Blood Institute. 9-1-1: Rapid identification and treatment of acute myocardial infarction. US Department of Health and Human Services, Public Health Service, National Institutes of Health 1994; May (NIH Publ. No. 94-3302).
3. Herlitz J, Blohm M, Hartford M, et al. Delay time in suspected acute myocardial infarction and the importance of its modification. Clin Cardiol 1989; 12:370–374.
4. Schroeder JS, Lamb IH, Hu M. The prehospital course of patients with chest pain. Analysis of the prodromal symptomatic, decision-making, transportation and emergency room period. Am J Med 1978; 64:742–746.
5. Hofgren K, Bondestam E, Johansson FG, et al. Initial pain course and delay to hospital admission in relation to myocardial infarct size. Heart Lung 1988; 17:274–280.
6. Ho MT, Eisenberg MS, Litwin PE, et al. Delay between onset of chest pain and seeking medical care: the effect of public education. Ann Emerg Med 1989; 18:727–731.
7. Sharkey SW, Brunette DD, Ruiz E, et al. An analysis of time delays preceding thrombolysis for acute myocardial infarction. JAMA 1989; 262:3171–3174.
8. Gonzalez ER, Jones LA, Ornato JP, et al. Hospital delays and problems with thrombolytic administration in patients receiving thrombolytic therapy: A multicenter prospective assessment. Ann Emerg Med 1992; 21: 1215–1221.
9. Kline EM, Smith DD, Martin JS, et al. In-hospital treatment delays in patients treated with thrombolytic therapy: A report of the GUSTO time to treatment substudy [abstract]. Circulation 1992; 86(4 Suppl 1):1.

10. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986; 1:397–402.
11. Fibrinolytic Therapy Trialists Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994; 343:311–322.
12. Guidelines for the early management of patients with acute myocardial infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (subcommittee to develop guidelines for the early management of patients with acute myocardial infarction). J Am Coll Cardiol 1990; 16:249–292.
13. MacCallum AG, Stafford PJ, Jones C, et al. Reduction in hospital time to thrombolytic therapy by audit of policy guidelines. Eur Heart J 1990; 11(Suppl F):48–52.
14. American Heart Association/Emergency Cardiac Care Committee and Subcommittees: Guidelines for cardiopulmonary resuscitation and emergency cardiac care, III: Adult advanced cardiac life support. JAMA 1992; 268:2199–2241.
15. Hossack KF, Hartwig R. Cardiac arrest associated with supervised cardiac rehabilitation. J Cardiac Rehabil 1982; 2:402–408.
16. Weaver WD, Cerqueira M, Hallstrom AP, et al. Prehospital-initiated vs. hospital-initiated thrombolytic therapy. The Myocardial Infarction Triage and Intervention Trial. JAMA 1993; 270:1211–1216.
17. The European Myocardial Infarction Project Group. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. N Engl J Med 1993; 329:383–389.
18. Gibler WB, Kereiakes DJ, Dean EN, et al. Prehospital diagnosis and treatment of acute myocardial infarction: A North-South perspective. The Cincinnati Heart Project and the Nashville Prehospital TPA Trial. Am Heart J 1991; 121:1–11.
19. Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block. N Engl J Med 1996; 334:481–493.
20. Apple FS. Acute myocardial infarction and coronary reperfusion. Am J Clin Pathol 1992; 97:217–226.
21. Sinkinson CA, Egherman WP, editors. Serum cardiac markers: Toward the earlier diagnosis of AMI. The University of Arizona College of Medicine. CME-TV Study Guide 1993; 4(2). p. 1–20.
22. Adams JE, Sicard GA, Allen BT. Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. N Engl J Med 1994; 330:670–674.
23. Ohman EM, Casey C, Bengtson JR, et al. Early detection of acute myocardial infarction: additional diagnostic information from serum concentrations of myoglobin in patients without ST elevation. Br Heart J 1990; 63:335–338.
24. Puleo PR, Meyer D, Wathen C, et al. Use of a rapid assay of subforms of creatinine kinase MB to diagnose or rule out acute myocardial infarction. N Engl J Med 1994; 331:561–566.
25. Sabia P, Afrookteh A, Touchstone DA, et al. Value of regional wall motion abnormality in the emergency room diagnosis of acute myocardial infarction: A prospective study using two-dimensional echocardiography. Circulation 1991; 84(Suppl I):85–92.
26. Cummins RO, editor. Textbook of Advanced Cardiac Life Support. Dallas, Texas; American Heart Association; 1994. p. 901–916.
27. Maroko PR, Radvany P, Braunwald E, Hale SL. Reduction of infarct size by oxygen inhalation following acute coronary occlusion. Circulation 1975; 52:360–368.
28. Madias JE, Hood WB. Reduction of precordial ST-segment elevation in patients with anterior myocardial infarction by oxygen breathing. Circulation 1976; 53:198–200.
29. Ishikawa K, Lee T, Ganz W. Effect of oxygen on perfusion and metabolism of the ischemic myocardium. J Appl Physiol 1974; 36:56–59.
30. Fillmore SJ, Shapiro M, Killip T. Arterial oxygen tension in acute myocardial infarction. Serial analysis of clinical state and blood gas changes. Am Heart J 1970; 79:620–629.
31. Patrono C. Aspirin as an antiplatelet drug. N Engl J Med 1994; 330:1287–1294.
32. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; 2:349–360.
33. Willard JE, Lange RA, Hillis LD. The use of aspirin in ischemic heart disease. N Engl J Med 1992; 327:175–181.
34. Hennekens CH, Jonas MA, Buring JE. The benefits of aspirin in acute myocardial infarction. Arch Intern Med 1994; 154:37–39.
35. Roux S, Christeller S, Ludin E. Effects of aspirin on coronary reocclusion and recurrent ischemia after thrombolysis: A meta-analysis. J Am Coll Cardiol 1992; 19:671–677.
36. Popma JJ, Topol EJ. Adjuncts to thrombolysis for myocardial reperfusion. Ann Intern Med 1991; 115:34–44.
37. Brown BG, Bolson E, Petersen RB, et al. The mechanism of nitroglycerin action: Stenosis vasodilatation as a major component of the drug response. Circulation 1981; 64:1089–1097.
38. Yusef S, Collins R, MacMahon S, Peto R. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomised trials. Lancet 1988; 1:1088–1092.
39. Jugdutt BI, Warnica JW. Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications. Effect of timing, dosage, and infarct location. Circulation 1988; 78:906–919.
40. Stockman MB, Verrier RL, Lown B. Effect of nitroglycerin on vulnerability to ventricular fibrillation during myocardial ischemia and reperfusion. Am J Cardiol 1979; 43:233–238.
41. Kinch JW, Ryan TJ. Right ventricular infarction. N Engl J Med 1994; 330:1211–1217.
42. Come PC, Pitt B. Nitroglycerin-induced severe hypotension and bradycardia in patients with acute myocardial infarction. Circulation 1976; 54:624–628.
43. Herlitz J. Analgesia in myocardial infarction. Drugs 1989; 37:939–944.
44. Lester R. Achieving pain relief with physiologic management and analgesic agents during acute myocardial

infarction. In: Califf RM, Wagner GS, eds. Acute Coronary Care: Principles and Practice. Boston: Martinus Nijhoff; 1985: 299–309.

45. Zelis R, Mansour EJ, Capone RJ, Mason DT. The cardiovascular effects of morphine; the peripheral capacitance and resistance vessels in human subjects. J Clin Invest 1974; 54:1247–1258.
46. Fibrinolytic Therapy Trialists; (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994; 343:311–322.
47. Rogers WJ, Bowlby LJ, Chandra NC, et al. Treatment of myocardial infarction in the United States (1990 to 1993). Observations from the National Registry of Myocardial Infarction. Circulation 1994; 90:2103–2114.
48. Weaver WD, Litwin PE, Martin JS, et al. Effect of age on use of thrombolytic therapy and mortality in acute myocardial infarction. The MITI Project Group. J Am Coll Cardiol 1991; 18:657–662.
49. Maggioni AP, Maseri A, Fresco C, et al. Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis. The Investigators of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2). N Engl J Med 1993; 329:1442–1448.
50. Gurwitz JH, Gore JM, Goldberg RJ, et al. Recent age-related trends in the use of thrombolytic therapy in patients who have had acute myocardial infarction. Ann Intern Med 1996; 124:283–291.
51. Krumholz HM, Pasternak RC, Weinstein MC, et al. Cost effectiveness of thrombolytic therapy with streptokinase in elderly patients with suspected acute myocardial infarction. N Engl J Med 1992; 327:7–13.
52. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6-24 hours after onset of acute myocardial infarction. Lancet 1993; 342:759–766.
53. Anderson HV, Willerson JT. Thrombolysis in acute myocardial infarction. N Engl J Med 1993; 329:703–709.
54. EMERAS (Estudio Multicentrico Estreptoquinasa Repulicas de America del Sur) Collaborative Group. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. Lancet 1993; 342: 767–772.
55. Grines CL, DeMaria AN. Optimal utilization of thrombolytic therapy for acute myocardial infarction: concepts and controversies. J Am Coll Cardiol 1990; 16: 223–231.
56. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation 1994; 89:1545–1556.
57. Freeman MR, Langer A, Wilson RF, et al. Thrombolysis in unstable angina: randomized double-blind trial of t-PA and placebo. Circulation 1992; 85:150–157.
58. Cragg DR, Friedman HZ, Bonema JD, et al. Outcome of patients with acute myocardial infarction who are ineligible for thrombolytic therapy. Ann Intern Med 1991; 115:173–177.
59. Califf RM, Fortin EF, Tenaglia AN, Sane DC. Clinical risks of thrombolytic therapy. Am J Cardiol 1992; 69: 12A–20A.
60. Maggioni AP, Franzosi MJ, Santoro E, et al. (GISSI-2) The risk of stroke in patients with acute myocardial infarction after thrombolytic and antithrombolytic treatment. N Engl J Med 1992; 327:1–6.
61. De Jaegere PP, Arnold AA, Balk AH, Simoons ML. Intracranial hemorrhage in association with thrombolytic therapy: incidence and clinical predictive factors. J Am Coll Cardiol 1992; 19:289–294.
62. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: A randomised comparison of streptokinase vs. tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet 1992; 339:753–770.
63. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329:673–682.
64. Mark DB, Hlatky MA, Califf RM, et al. Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. N Engl J Med 1995; 332:1418–1424.
65. Landau C, Lange RA, Hillis LD. Percutaneous transluminal coronary angioplasty. N Engl J Med 1994; 330: 981–993.
66. Topol EJ, Califf RM, George BS, et al. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987; 317:581–588.
67. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) phase II trial. N Engl J Med 1989; 320:618–627.
68. Zijlstra F, de Boer MJ, Hoorntje JC, et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993; 328:680–684.
69. Gibbons RJ, Holmes DR, Reeder GS, et al. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med 1993; 328: 685–691.
70. Stone GW, Rutherford BD, McConahay DR, et al. Direct coronary angioplasty in acute myocardial infarction: outcome in patients with single vessel disease. J Am Coll Cardiol 1990; 15:534–543.
71. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1993; 328:673–679.
72. Michels KB, Yusuf S. Does PTCA in acute myocardial infarction affect mortality and reinfarction rates? A quantitative overview (meta-analysis) of the randomized clinical trials. Circulation 1995; 91:476–485.
73. The MIAMI Trial Research Group. Metoprolol in acute myocardial infarction. Patient population. Am J Cardiol 1985; 56:1G–57G.
74. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. Lancet 1986; 2:57–66.
75. Viscoli CM, Horowitz RI, Singer BH. Beta-blockers after myocardial infarction: influence of first-year clinical course on long-term effectiveness. Ann Intern Med 1993; 118:99–105.

76. Hirsh J. Heparin. N Engl J Med 1991; 324:1565–1574.
77. Hirsh J, Fuster V. Guide to anticoagulant therapy. Part 1: Heparin: American Heart Association. Circulation 1994; 89:1449–1468.
78. Neri Serneri GG, Gensini GF, Poggesi L, et al. Effect of heparin, aspirin, or alteplase in reduction of myocardial ischaemia in refractory unstable angina. Lancet 1987; 1:937–942.
79. Randomised controlled trial of subcutaneous calcium-heparin in acute myocardial infarction: The SCATI (Studio sulla Calciparina nell'Angina e nella Trombosi Ventricolare nell'Infarto) Group. Lancet 1989; 2:182–186.
80. Col J, Decoster O, Hanique G, et al. Infusion of heparin conjunct to streptokinase accelerates reperfusion of acute myocardial infarction: results of a double blind randomized study (OSIRIS) [abstract]. Circulation 1992; 86(suppl 1):1.
81. O'Connor CM, Meese R, Carney R, et al. A randomized trial of intravenous heparin in conjunction with anistreplase (anisoylated plasminogen streptokinase activator complex) in acute myocardial infarction: the Duke University Clinical Cardiological Study (DUCCS)1. J Am Coll Cardiol 1994; 23:11–18.
82. GISSI-2: A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Lancet 1990; 336:65–71.
83. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329:1615–1622.
84. Bleich SD, Nichols TC, Schumacher RR, et al. Effect of heparin on coronary arterial patency after thrombolysis with tissue plasminogen activator in acute myocardial infarction. Am J Cardiol 1990; 66:1412–1417.
85. Chesebro JH, Fuster V. Antithrombotic therapy for acute myocardial infarction: mechanisms and prevention of deep venous, left ventricular, and coronary artery thromboembolism. Circulation 1986; 74(Suppl III):1–10.
86. The International Study Group. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. Lancet 1990; 336:71–75.
87. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular weight heparin or unfractionated heparin. N Engl J Med 1995; 332:1330–1335.
88. De Bono DP, Simoons ML, Tijssen J, et al. Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: Results of a randomised double blind European Cooperative Study Group trial. Br Heart J 1992; 67: 122–128.
89. Lee LV. Initial experience with hirudin and streptokinase in acute myocardial infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) 6 trial. Am J Cardiol 1995; 75:7–13.
90. Cannon CP, McCabe CH, Henry TD, et al. A pilot trial of recombinant desulfatohirudin compared with heparin in conjunction with tissue-type plasminogen activator and aspirin for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 5 trial. J Am Coll Cardiol 1994; 23:993–1003.
91. Antman EM. Hirudin in acute myocardial infarction. Safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A Trial. Circulation 1994; 90:1624–1630.
92. Topol EJ, Fuster V, Harrington RA, et al. Recombinant hirudin for unstable angina pectoris. A multicenter, randomized angiographic trial. Circulation 1994; 89: 1557–1566.
93. Sirnes PA, Overskeid K, Pedersen TR, et al. Evolution of infarct size during the early use of nifedipine in patients with acute myocardial infarction: The Norwegian Nifedipine Multicenter Trial. Circulation 1984; 70:638–644.
94. Secondary prevention reinfarction Israeli nifedipine trial (SPRINT). A randomized intervention trial of nifedipine in patients with acute myocardial infarction. The Israeli Spring Study Group. Eur Heart J 1988; 9:354–364.
95. Goldbourt U, Behar S, Reicher-Reiss H, et al. Early administration of nifedipine in suspected acute myocardial infarction. The Secondary Prevention Reinfarction Israel Nifedipine Trial 2 Study. Arch Intern Med 1993; 153:345–353.
96. The Danish Study Group on Verapamil in Myocardial Infarction. Verapamil in acute myocardial infarction. Eur Heart J 1984; 5:516–528.
97. Boden WE, Krone RJ, Kleiger RE, et al. Electrocardiographic subset analysis of diltiazem administration on long-term outcome after acute myocardial infarction. The Multicenter Diltiazem Post-Infarction Trial Research Group. Am J Cardiol 1991; 67:335–342.
98. Boden WE, Scheldewaert R, Walters EG, et al. for the Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Thrombolysis (diltiazem) (INTERCEPT) Research Group. Design of a placebo-controlled clinical trial of long-acting diltiazem and aspirin versus aspirin alone in patients receiving thrombolysis with a first acute myocardial infarction. Am J Cardiol 1995; 75:1120–1123.
99. Rongione AJ, Isner JM. Cocaine-induced contraction of vascular smooth muscle is inhibited by calcium channel blockers [Abstract]. J Am Coll Cardiol. 1989; 13: 78A.
100. Minor RL, Scott BD, Brown DD, Winniford MD. Cocaine-induced myocardial infarction in patients with normal coronary arteries. Ann Intern Med 1991; 115:797–806.
101. Magrini F, Feggiani P, Roberts N, et al. Effects of angiotensin and angiotensin blockade on coronary circulation and coronary reserve. Am J Med 1988; 84(suppl. 3A):55–60.
102. Swedberg K, Held P, Kjekshus J, et al., on behalf of the CONSENSUS II Study Group. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). N Engl J Med 1992; 327:678–684.
103. ISIS-4 (Fourth International Study Group of Infarct Survival) Collaborative Group. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet 1995; 345:669–685.
104. Gruppo Italiano per lo Studio della Sopravvivenza

nell'Infarto Miocardico. GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet 1994; 343: 1115–1122.

105. Woods KL. Possible pharmacological actions of magnesium in acute myocardial infarction. Br J Clin Pharmacol 1991; 32:3–10.
106. Iseri LT, French JH. Magnesium: Nature's physiologic calcium blocker. Am Heart J 1984; 108:188–193.
107. Arsenian MA. Magnesium and cardiovascular disease. Prog Cardiovasc Dis 1993; 35:271–310.
108. Woods KL, Fletcher S, Roffe C, Haider Y. Intravenous magnesium sulphate in suspected acute myocardial infarction: Results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). Lancet 1992; 339:1553–1558.
109. Woods KL, Fletcher S. Long-term outcome after intravenous magnesium sulphate in suspected acute myocardial infarction: the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). Lancet 1994; 343:816–819.
110. Shecter M, Hod H, Couraqui P, et al. Magnesium therapy in acute myocardial infarction when patients are not candidates for thrombolytic therapy. Am J Cardiol 1995; 75:321–323.
111. Tzivoni D, Banai S, Schuger C, et al. Treatment of torsade de pointes with magnesium sulfate. Circulation 1988; 77:392–397.
112. DeWood MA, Notske RN, Hensley GR, et al. Intraaortic balloon counterpulsation with and without reperfusion for myocardial infarction shock. Circulation 1980; 61: 1105–1112.
113. Leinbach RC, Gold HK, Harper RW, et al. Early intraaortic balloon pumping for anterior myocardial infarction without shock. Circulation 1978; 58:204–210.
114. Ohman EM, Califf RM, George BS, et al., and The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group. The use of intraaortic balloon pumping as an adjunct to reperfusion therapy in acute myocardial infarction. Am Heart J 1991; 121: 895–901.
115. Ohman EM, George BS, White CJ, et al., for the Randomized IABP Study Group. Use of aortic counterpulsation to improve sustained coronary artery patency during acute myocardial infarction. Results of a randomized trial. Circulation 1994; 90:792–799.
116. Lee L, Bates ER, Pitt B, et al. Percutaneous transluminal coronary angioplasty improves survival in acute myocardial infarction complicated by cardiogenic shock. Circulation 1988; 78:1345–1351.
117. Hochman JS, Boland J, Sleeper LA, et al., and the SHOCK Registry Investigators. Current spectrum of cardiogenic shock and effect of early revascularization on mortality. Results of an International Registry. Circulation 1995; 91:873–881.
118. Campbell RWF, Murray A, Julian DG. Ventricular arrhythmias in first 12 hours of acute myocardial infarction. Natural history study. Br Heart J 1981; 46:351–357.
119. Volpi A, Cavalli A, Santoro E, Tognoni G, and GISSI Investigators. Incidence and prognosis of secondary ventricular fibrillation in acute myocardial infarction. Evidence for a protective effect of thrombolytic therapy. Circulation 1990; 82:1279–1288.
120. Antman EM, Berlin JA. Declining incidence of ventricular fibrillation in myocardial infarction. Implications for the prophylactic use of lidocaine. Circulation 1992; 86:764–773.
121. Campbell RWF, Julian D, Braunwald E, editors. Management of Acute Myocardial Infarction. London: W. B. Saunders; 1994: Arrhythmias, pp. 223–240.
122. MacMahon S, Collins R, Peto R, et al. Effects of prophylactic lidocaine in suspected acute myocardial infarction. An overview of results from the randomized, controlled trials. JAMA 1988; 260:1910–1916.
123. Antman EM, Julian D, Braunwald E, editors. Management of Acute Myocardial Infarction. London: W. B. Saunders; 1994: General hospital management, pp. 57–59.
124. Berger PB, Ruocco NA Jr., Ryan TJ, et al., and the TIMI Investigators. Incidence and prognostic implications of heart block complicating inferior myocardial infarction treated with thrombolytic therapy: results from TIMI II. J Am Coll Cardiol 1992; 20:533–540.
125. Nicod P, Gilpin E, Dittrich H, et al. Long-term outcome in patients with inferior myocardial infarction and complete atrioventricular block. J Am Coll Cardiol 1988; 12:589–594.
126. Cummins RO, editor. Textbook of Advanced Cardiac Life Support. Dallas, Texas: American Heart Association; 1994. p. 701–721.
127. Varriale P, Inguaggiato A, David W. Bradyarrhythmias incident to thrombolysis for acute interior wall infarction. A caveat. Chest 1992; 101:732–735.
128. Kent KM, Smith ER, Redwood DR, et al. Electrical stability of acutely ischemic myocardium; influences of heart rate and vagal stimulation. Circulation 1973; 47: 291–294.
129. Massumi RA, Manson DT, Amsterdam EA, et al. Ventricular fibrillation and tachycardia after intravenous atropine for treatment of bradycardias. N Engl J Med 1972; 287:336–338.
130. Zoll PM, Zoll RH, Falk R, et al. External noninvasive temporary cardiac pacing clinical trials. Circulation 1985; 71:937–944.
131. Hynes JK, Holmes DR, Jr, Harrison CE. Five-year experience with temporary pacemaker therapy in the coronary care unit. Mayo Clin Proc 1983; 58:122–126.
132. Collen D, Stassen JM, Yasuda T, et al. Comparative thrombolytic properties of tissue-type plasminogen activator inhibitor-1-resistant glycosylation variant, in a combined arterial and venous thrombosis model in the dog. Thromb Haemostasis 1994; 72:98–104.
133. Neuhaus KL, von Essen R, Vogt A, et al. Dose finding with a novel recombinant plasminogen activator (BM 06.022) in patients with acute myocardial infarction: Results of the German Recombinant Plasminogen Activator Study. J Am Coll Cardiol 1994; 24:55–60.
134. Samama MM, Acar J. Thrombolytic therapy: Future issues. Thromb Haemostasis 1995; 74:106–110.
135. Coller BS. Blockade of platelet GPIIb/IIIa receptors as an antithrombotic strategy. Circulation 1995; 92: 2373–2380.
136. Coller BS, Anderson K, Weisman HF. New antiplatelet agents: platelet GPIIb/IIIa antagonists. Thromb Haemostasis 1995; 74:302–308.
137. Popma JJ, Coller BS, Ohman EM, et al. Antithrombotic therapy in patients undergoing coronary angioplasty. Chest 1995; 108(Suppl):486S–501S.
138. Muller-Bardorff M, Freitag H, Scheffold T, et al. Development and characterization of a rapid assay for bedside determination of cardiac troponin T. Circulation 1995; 92:2869–2875.

139. De Winter RJ, Koster RW, Sturk A, Sanders GT. Value of myoglobin, troponin T, and CK-Mb$_{\text{mass}}$ in ruling out an acute myocardial infarction in the emergency room. Circulation 1995; 92:3401–3417.
140. Bhayana V, Cohoe S, Pellar TG, et al. Combination (multiple) testing for myocardial infarction using myoglobin, creatine kinase-2 (mass), and troponin T. Clin Biochem 1994; 27:395–406.
141. Murray C, Alpert JS. Diagnosis of acute myocardial infarction. Curr Opin Cardiol 1994; 9:465–470.
142. Peterson KF, Head WM. Emergency room liability. Trial Lawyers Q 1995/96; 26:18–24.
143. McGovern PG, Pankow JS, Shahar E, et al., for the Minnesota Heart Survey Investigators. Recent trends in acute coronary heart disease. N Engl J Med 1996; 334:884–890.

Management of Life-Threatening Asthma in the Emergency Department

LYNNE RICHARDSON, M.D.,[1] AND ANDY JAGODA, M.D.[2]

Abstract

Acute asthma exacerbations are frequent presentations to the emergency department. Those patients who deteriorate despite nebulized β-agonist therapy and intravenous steroids are experiencing a life-threatening event. They pose a significant management challenge to the emergency physician. This review describes the pharmacologic options and techniques for mechanical ventilation which are available in resuscitating these patients.
Key Words: asthma, near-fatal asthma, status asthmaticus, β-agonists, ketamine, mechanical ventilation.

DESPITE ADVANCES in our understanding of the pathophysiology of asthma, and improvements in our therapeutic pharmacopoeia, many patients with severe asthma continue to present to the emergency department (ED). An estimated 5% of Americans have reactive airway disease; acute exacerbations result in approximately two million ED visits annually and 5,000 deaths (1–3). The incidence of severe asthma attacks and the rate of asthma-related death are increasing (3–5). Up to 5% of the patients with asthma will at some time have a severe exacerbation of their disease (6–8).

Acute asthma exacerbations are graded according to severity based on clinical and laboratory parameters (3). Patients with asthma exacerbations of moderate severity are alert, are able to speak in phrases, are wheezing with an oxygen saturation at 90 to 95%, have a pCO_2 less than 40 mm Hg, and have a peak expiratory flow (PEFR) of greater than 50% of predicted. An asthma attack graded as severe indicates significant impairment of air flow with possible mental status alteration and cyanosis, decreased breath sounds, oxygen saturation less than 90%, pCO_2 greater than 40 mm Hg, or a PEFR less than 25% of predicted (3). Patients with severe disease who deteriorate despite β-agonist and steroid therapy need aggressive and intensive interventions. However, there are no clear guidelines in the literature for managing these cases.

The purpose of this article is to give a brief overview of the factors associated with the increase in the morbidity and mortality caused by asthma, and to discuss the acute management of patients with life-threatening exacerbations of their asthma.

Epidemiology

For the past two decades, the prevalence of asthma, as well as the rates of hospitalizations and deaths caused by asthma have been increasing (9, 10). Table 1 lists factors that are thought to contribute to this increase. Historical risk factors for severe exacerbations include frequently recurring attacks, frequent ED visits, less than a 10-year history of asthma, systemic corticosteroid use for asthma in the previous year, smoking, and poor out-patient surveillance (3, 7, 11, 12). Additional indicators of potential airway instability in-

---

From the Department of Emergency Medicine, Mount Sinai School of Medicine, New York, NY. [1]FACEP, Emergency Medicine Residency Program Director. [2]FACEP, Associate Professor of Emergency Medicine. Address correspondence to Lynne Richardson, M.D., Department of Emergency Medicine, The Mount Sinai School of Medicine, Box 1149, One East 100th Street, New York, NY 10029.

TABLE 1

Factors Related to Asthma Morbidity and Mortality

Prior life-threatening episodes
Hospitalization within the last year
Lack of access to primary care
Over-reliance on β-agonists
Underutilization of anti-inflammatory agents
Failure to diagnose and monitor individual patient's conditions
Failure to recognize illness severity
Failure to adequately educate patients
Failure to prospectively develop a strategy to deal with disease exacerbations

clude short-lived relief from inhaled bronchodilators, worsening of symptoms from viral illness, nighttime flare-ups, and a history of intubation. A history of intubation is the strongest single predictor of subsequent death from asthma (13, 14). In one study of asthmatics requiring intubation, 16.5% died while in the hospital, and 23% died of their asthma within 6 years (7). It was recently reported that patients at risk for near-fatal asthma attacks have a reduced hypoxic drive and a blunted perception of dyspnea (15).

The increases in asthma prevalence, morbidity, and mortality have not been uniformly distributed across the population. Increases have been markedly higher in children and young adults. In this country, urban areas have a higher prevalence and account for a disproportionate number of asthma hospitalizations and deaths. Recent studies have identified certain subpopulations who are at high risk for asthma morbidity and mortality. Blacks and Hispanics have a somewhat higher prevalence of asthma, but a several fold difference in hospitalization and mortality (16). Poverty has also been associated with higher rates of asthma and increased asthma morbidity. Some authors have suggested that race is a proxy for low socioeconomic status and that race/ethnicity differences disappear after controlling for socioeconomic status, but more recent studies show that race/ethnicity and poverty exert independent effects on asthma prevalence, morbidity, and mortality (16, 17).

Considerable controversy exists regarding the association between β-agonist use and asthma morbidity (18, 19). Spitzer et al. (20) and Ernst et al. (21) reported an increased risk of death associated with use of inhaled β-agonist which was independent of disease severity. However, a meta-analysis of β-agonist use and death from asthma found only a very weak relation between nebulized β-agonist use and death. There was no association between metered dose inhaler or oral β-agonist use and death, although the mean age of patients in Spitzer's group was older than those in the meta-analysis sample, 32 versus 25.3 years, respectively (22). Despite the controversy regarding the long-term impact of chronic inhaled β-agonists use, there is no argument that they play a crucial role in the management of acute asthma exacerbations.

β-Adrenergic Agents

The β-agonists are the first-line therapy in managing acute asthma attacks (3). Various β-agonists are available, although the β_2-selective agents are preferred and can be inhaled or given intravenously, subcutaneously, or endotracheally.

Inhalation is preferred over subcutaneous administration. In most cases, the inhaled route is equally as effective as the subcutaneous route, lasts longer, and avoids the discomfort of an injection (23). Subcutaneous administration may be preferred when air flow is so compromised that it precludes inhaled delivery. Both epinephrine and terbutaline can be given subcutaneously with similar onset of action, equivalent subjective and objective improvement in pulmonary function, and the same adverse effect profile (24). Neither drug has been associated with life-threatening dysrhythmias or hypertension when used to treat asthma. In fact, blood pressure, respiratory rate, and heart rate all decrease with treatment, even when used in the elderly or patients with known coronary disease (25).

Nebulized terbutaline, metaproterenol, and albuterol are all acceptable and dosed according to patient response; a patient with severe asthma may be given continuous administration (3, 26). Metered dose inhalers (MDI) are effective in mild to moderate attacks but depend on optimum conditions ensuring full delivery and therefore should not be used in severe attacks (26). An alternative to intermittent nebulization treatments is continuous treatment in which double or triple the single dose of medication is given for 45 to 120 minutes (27–29). Continuous treatments have been effective and safe even in patients with underlying cardiac disease. Some concern has been raised over continuous β-agonist nebulizations inducing serum electrolyte alterations (30, 31). One study documented decreases in the serum potassium levels averaging 0.53 mEq/L after two to five albuterol treatments (30). The clinical importance of the change of electrolytes is undetermined, but β-agonist-induced hypokalemia or cardiotoxicity is not thought to play a role in the increased incidence of asthma-related mortality.

Intravenous β-agonist agents have been used primarily in children for managing severe exacerbations that are refractory to initial treatment. In one study, 77% of children who were candidates for intubation improved with intravenous isoproterenol (32). A similar experience has been reported with intravenous salbutamol. There have been no drug-related deaths attributed to the use of isoproterenol in the pediatric asthma population. One asthmatic adult was reported to have died of intravenous isoproterenol (33). The use of intravenous terbutaline is recommended in the management of deteriorating, severe cases. A loading dose of 10 μg/kg over 10 minutes should be followed by an infusion beginning at 0.4 μg/kg/min and increased as needed to a rate of 3–6 μg/kg/min (3, 34).

There is one report of albuterol given endotracheally; 2.5 mg in 2.5 cc saline was followed by 5 mg 25 minutes later, with significant improvement in respiratory function resulting in extubation (35). As little as 20% of nebulized β-agonists reach the bronchial tree under the best of circumstances (26). Therefore, for certain cases, direct endotracheal instillation may be preferred, although this needs to be studied further.

Anticholinergic Agents

Bronchoconstriction can be accentuated by increased vagal tone. The vagolytics atropine, ipratropium bromide, and glycopyrolate have been used to treat bronchospasm but have not been found to be superior to the β-agonists when used alone. Their effect may be additive when used in conjunction with the β-agonists (36, 37). The vagolytics are usually administered via nebulization, although intravenous glycopyrolate, 0.2 mg, has been reported to be successful as a third-line drug in refractory cases (38).

Methylxanthines

Aminophylline, which is recommended in many management algorithms for the hospitalized asthma patient (3, 34, 39), does not have a proven role in the stabilization of acute bronchospasm (12, 40, 41). There is one study by Wrenn et al. (42) that challenges this conclusion, although lack of control in the study's design and subjective variables make the study's findings unconvincing. The role of methylxanthines in long-term management continues to be controversial (43, 44). Mechanisms of action of aminophylline include bronchodilation, enhancement of mucociliary clearance, decrement of microvascular permeability in the airway mucosa, elevation of the level of circulating catecholamines, and enhancement of diaphragmatic contractility (45). Its value in management of chronic asthma may be in modulating the late phase of the disease, thus containing inflammation and edema. In a study by Nassif et al. (43) the use of theophylline decreased the need for β-agonists and steroids in the maintenance therapy of asthma patients.

Corticosteroids

The corticosteroids are used to modulate the inflammatory response associated with both acute and chronic asthma (3, 46, 47). Although the onset of action occurs between 4 and 8 hours, the early initiation of steroids decreases the incidence of relapse, which supports their use early in management (46, 48, 49). In one study, when steroids were added to inhaled β-agonist therapy, the incidence of hospitalization decreased from 47% to 19% (48).

Magnesium

The utility of magnesium sulfate ($MgSO_4$) in managing severe asthma is controversial, although a growing amount of literature supports its use in asthma resuscitation (50–53). Its proposed mechanism is through smooth muscle relaxation and possibly via mast cell stabilization (54). It is usually administered in a single dose given as an intravenous infusion over 20 to 30 minutes. In one study, six patients who were refractory to β-agonists, steroids, and aminophylline had significant improvement after an infusion of 3.0 g of magnesium sulfate administered over 20 minutes (55). In a placebo-controlled, double-blind trial of 38 patients with moderate to severe acute asthma, a significant increase in PEFR was demonstrated after the infusion of 1.2 g $MgSO_4$ (56). A recent report by Bloch et al. (53) reported a improvement in the FEV_1 and a decrease in admission rate of patients with severe asthma as the result of a 2 g infusion. Similar results are reported in the pediatric literature using infusions of 40 mg/kg (57). Not all studies with magnesium have shown a benefit (58, 59). However, magnesium is relatively safe and may be a reasonable consideration in the management of severe disease.

Anesthesia

Both inhalational and intravenous anesthetics have roles in the management of patients with severe asthma who deteriorate. Ketamine is an intravenous general anesthetic agent with bronchodilating properties (60–62). It causes minimal myocardial depression, but does stimulate the cardiovascular system and must be used with caution in patients with hypertension and ischemic cardiac disease. Because it increases bronchial secretions, it is usually administered with an anticholinergic agent such as atropine or glycopyrrolate (63). The most controversial adverse effect is the induction of hallucinations, especially in adults, which can be minimized by premedication with benzodiazepines (63). Ketamine has been successful in the management of severe asthma in both pediatric (64, 65) and adult populations (66).

Many of the inhalation anesthetics, including halothane, isoflurane, enflurane, and ether, are potent bronchodilators and have been successfully used in managing severe asthma (67–70). Unfortunately, the logistics of using inhalational agents in the ED often precludes their use. Helium-oxygen mixture (60%He/40%O) has been demonstrated to be effective in improving oxygenation in severe asthma exacerbations (71). Helium is an inert gas of low molecular weight which enhances laminar flow, reduces the work of breathing, decreases airway resistance, and allows for greater oxygen delivery.

Management

Patients presenting with severe asthma are initially stabilized by simultaneously gaining intravenous access, establishing cardiac and pulse oximetry monitoring, and instituting bronchodilator and steroid therapy. Pulse oximetry is useful as a guide for oxygen therapy, but it must be recognized that it does not monitor hypercarbia which may be of critical concern in these patients. Blood gas analysis is indicated when the pulse oximetry reflects desaturation below 90% which does not correct with oxygen and nebulization treatments, or when there is evidence of clinical deterioration. A pCO_2 of 40 mm Hg or greater is an indicator of ventilatory failure and may suggest a need for intubation; however, patients with significant hypercapnia have been managed successfully without intubation (72, 73).

Most patients presenting to the ED with asthma respond to β-agonist nebulization treatments. Those patients who do not respond are likely to have had bronchospasm of some duration and have developed significant inflammation and airway edema. In these patients, consideration must be given to additional therapies that include anticholinergics, theophylline, magnesium, ketamine, and intravenous β-agonists. (See Table 2.)

Children younger than 12 years of age with refractory disease who are clinically deteriorating are candidates for ketamine after premedication with a vagolytic. If there is no improvement, intravenous β-agonists may be tried. The safety of ketamine and intravenous β-agonists in adults has not been proven, but in severe cases the potential benefit of these agents may outweigh the risks.

Patients who develop mental status changes, hypoxia, or show signs of fatigue with impending respiratory failure must be evaluated for intubation and mechanical ventilation. Hypercapnia and hypoxia alone are not absolute indications for intubation. The patient's clinical state and response to treatment is taken into consideration, because mechanical ventilation has potential consequences that can contribute to mortality including hypotension, lobar collapse, pneumomediastinum, and pneumothoraces (13, 74, 75).

Implementing the decision to intubate must involve a clinician who is experienced in managing the difficult airway. The preferred method will depend on the specific clinical circumstances; nasotracheal intubation with local anesthesia, awake oral intubation, and rapid sequence intubation all have their place in airway management of patients with asthma. Proper precautions must be taken in preparation for all potential outcomes, including an unsuccessful initial attempt.

Once intubated, the goal of mechanical ventilation is to ensure oxygenation without producing iatrogenic barotrauma (see Table 3). This is accomplished through the use of controlled hypoventilation with permissive hypercapnea; patients are ventilated at low volumes and at slow rates to minimize airway pressures, thus avoiding barotrauma. Controlled hypoventilation does not focus on correcting the $PaCO_2$; hypercapnea will often correct itself once oxygenation is improved and the patient's work of breathing decreases (74, 76). A volume-cycled ventilator is best used, set at a low inspiratory pressure, and a slow respiratory rate with an I/E ratio of at least 1:3. Positive end-expiratory pressure is generally avoided. The respiratory rate in adults is initially set at 8 to 10 (higher in young children and infants) with a tidal volume of 5 to 7 cc/kg and insufflation pressures kept less than 35 cm H_2O (76). A volume-cycled respirator ensures a tidal volume that is constant despite fluctuating airway pressures (8); the rate and volume are adjusted to keep the peak pressures below desired levels. If this alone does not work, sedation or paralysis is indicated. In severe cases, pressure

TABLE 2
Medications in Acute Asthma Management

Route and medication	Adult dose	Pediatric dose
Subcutaneous		
Epinephrine	0.3–0.5 mL 1:1000 aqueous soln	0.01 mL/kg/dose 1:1000, **max** dose 0.3 mL/kg/dose
Terbutaline	0.25 mg	0.01 mg/kg, **max** dose 0.4 mg
Inhalation		
Albuterol	2.5–5 mg in 2 mL NS[a] every 20 min or 10 mg/7.5 mL NS continuously	2.5 mg if <10 kg 5.0 mg if >10 kg or 0.1–0.3 mg/kg/hr continuously
Terbutaline	2–5 mg in 2 mL NS	
Metaproterenol	10–15 mg in 2.5 mL NS	5–15 mg
Atropine	2.5 mg in 2.5 mL NS	0.01–0.03 mL/kg in 2.5 mL NS every 3–4 hr, **max** dose 1.0 mg
Iprotroprium	500 μg in 2.5 mL NS	250 μg every 3–6 hr
Glycopyrrolate	2 mg in 2 mL NS	1 mg diluted in 2 mL of 0.45% saline
Intravenous		
Methylprednisolone	125 mg	2 mg/kg, then 1–2 mg/kg/dose every 6 hr
Magnesium sulfate	2–4 g over 10–20 min	30–70 mg/kg over 20 min; **max** dose 1 g
Aminophylline	5–6 mg/kg then 0.6–0.9 mg/kg/hr	Same loading as adults maintenance 1 mg/kg/hr
Severe asthma		
Isoproterenol	0.5–5 μg/min	
Terbutaline	250 μg over 10 min, then 3–12 μg/min	Load 10 μg/kg over 30 min, then continuous infusion 0.1 μg/kg/min
Glycopyrrolate	0.2 mg	
Ketamine	0.2–1.5 mg/kg then 0.3–2 mg/kg/hr	0.5–2.0 mg/kg every hr or as continuous drip
Inhalation anesthesia		
Isoflurane		
Halothane		
Enflurane		
Ether		
Heliox (60–80% helium/ 20–40% oxygen)		

[a] NS, normal saline solution.

control ventilation is recommended. Ventilatory support and muscle relaxation are usually sufficient to reverse acidosis. When acidosis persists, some have recommended that giving bicarbonate be considered (72, 77, 78).

Once intubated, patients must be carefully observed for pneumothorax which has been reported in up to 18% of patients with asthma who have been intubated. Pneumothoraces account for much of the associated morbidity and mortality in these patients (79). Signs of pneumothorax include hypotension and a rapid increase in ventilator pressures.

Intubation secures the airway; however, it does not manage the underlying bronchospasm which poses a major problem in these patients. Less than 5% of nebulized agents reach the lungs when delivered through ventilator tubing (80–82). Delivery can be improved by increasing the volume of nebulizer fill, and by positioning the nebulizer between the Y-piece and catheter mount or on the inspiratory limb of the ventilator circuit Y-piece when jet nebulizers are used (81). Drug delivery must be carefully assessed and reassessed in the intubated patient and every effort must be made to chose therapies that maximize bronchodilation.

Conclusion

In conclusion, the prevalence, morbidity, and mortality of asthma are increasing. Those patients presenting to the emergency department with severe asthma attacks require an intensive resuscitative effort that minimizes the risks for iatrogenic harm. Nebulized β-agonists and intravenous steroids remain the first-line drugs in treating these patients. Patients whose condition deteriorates may benefit from intravenous magnesium sulfate, nebulized or intravenous vagolytics, or helium-oxygen administration. Third-line therapies for severe asthma include ketamine and intravenous β-agonists. If intubation and mechanical ventilation are required, permissive hy-

TABLE 3
Mechanical Ventilation in Severe Asthma

Considerations for intubation	
Hypoxemia	
$PaO_2 < 60$ mm Hg	
Altered mental status	
Fatigue	
Diaphoresis and patient position	
Hypercapnea and acidosis (There are no absolute values, see text.)	
Initial ventilator settings	
FiO_2	1.0
Ventilatory rate	8–10
Tidal volume	5–7 cc/kg
I/E Ratio[a]	At least 1:3
PEEP[b]	0
Ventilator considerations if peak pressures remain consistently above 40–50 cm H_2O	
Verify appropriate tube position	
Evaluate for pneumothorax, mucous plug	
Ensure sedation	
Neuromuscular paralysis	
Decrease rate and tidal volume	
Change to pressure cycled ventilation	

[a] I/E, inspiratory to expiratory ratio.
[b] PEEP, positive end-expiratory pressure.

poventilation is utilized; patients are ventilated with low volumes at slow rates to avoid the high airway pressures and lung overinflation that may result in potentially life-threatening complications.

References

1. Summer W, Status asthmaticus. Chest 1985; 87 (suppl): 87S–94S.
2. Centers for Disease Control. Asthma: United States 1982–1992. JAMA 1995; 273:451–452.
3. National Asthma Education Program. Guidelines for the diagnosis and management of asthma. National Institutes of Health, Publication No. 91-3042, 1991; 1–136.
4. Weiss K, Wagener D. Changing patterns of asthma mortality: Identifying target populations at high risk. JAMA 1990; 264:1683–1687.
5. Buist A, Vollmer W. Reflections on the rise in asthma morbidity and mortality. JAMA 1990; 264:1719–1720.
6. Dales R, Munt P. Use of mechanical ventilation in adults with severe asthma. Can Med Assoc J 1984; 130:391–394.
7. Marquette C, Saulnier F, Leroy O, et al. Long-term prognosis of near-fatal asthma. Am Rev Respir Dis 1992; 146:76–81.
8. Mansel J, Stogner S, Petrini M, Norman J. Mechanical ventilation in patients with acute severe asthma. Am J Med 1990; 89:42–48.
9. Sly R. Mortality from asthma in children: 1979–1984. J Allergy Clin Immunol 1988; 82:705–717.
10. Gergen P, Weiss K. The increasing problem of asthma in the United States. Am Rev Respir Dis 1992; 146:823–824.
11. Richardson L, McLean D, et al. Factors associated with frequent ED use for asthma [abstract]. Acad Emerg Med 1996; 3:123.
12. Bone R, Calverley P, Chapman K, et al. The international clinical respiratory group: special report. Chest 1992; 101:1420–24.
13. Seddon P, Heaf D. Long term outcome of ventilated asthmatics. Arch Dis Child 1990; 65:1324–1327.
14. Rea HH, Scragg R, Jackson R, et al. A case control study of deaths from asthma. Thorax 1986; 41:833–839.
15. Kikuchi Y, Okabe S, Tamura G, et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. N Engl J Med 1994; 330:1329–1334.
16. Weiss K, Gergen P, Crain E. Inner city asthma: The epidemiology of an emerging public concern. Chest 1992; 101:362s–367s.
17. Findley SE, McLean DE, Stevens K. Interactive effects of race and poverty on asthma [abstract]. Am J Respir Dis Crit Care, 1996; PA429.
18. Skorodin M. Beta-adrenergic agonists: A problem. Chest 1993; 103:1587–1590.
19. Ziment I. Beta-adrenergic agonist toxicity: Less of a problem, more of a perception. Chest 1993; 103:1591–1597.
20. Spitzer W, Suissa S, Ernst P, et al. The use of beta-agonists and the risk of death and near death from asthma. N Engl J Med 1992; 326:501–506.
21. Ernst P, Habbick B, Suissa S, et al. Is the association between inhaled beta-agonist use and life-threatening asthma because of confounding by severity? Am Rev Respir Dis 1993; 148:75–79.
22. Mullen M, Mullen B, Carey M. The association between beta-agonist use and death from asthma: A meta-analytic integration of case-control studies. JAMA 1993; 270:1842–1845.
23. Becker A, Nelson N, Simons F. Inhaled salbutamol vs injected epinephrine in the treatment of acute asthma in children. J Pediatr 1983; 102:465–469.
24. Spiteri M, Millar A, Pavia D, Clarke S. Subcutaneous adrenaline versus terbutaline in the treatment of acute severe asthma. Thorax 1988; 43:19–23.
25. Cydulka R, Davison R, Grammar L, et al. The use of epinephrine in the treatment of older adult asthmatics. Ann Emerg Med 1988; 17:322–326.
26. Turner J, Corkery K, Eckman D, et al. Equivalence of continuous flow nebulizer and metered dose inhaler with reservoir bag for treatment of acute airflow obstruction. Chest 1988; 93:476–481.
27. Olshaker J, Jerrard D, Barish R, et al. The efficacy and safety of a continuous albuterol protocol for the treatment of acute adult asthma attacks. Am J Emerg Med 1993; 11:131–133.
28. Lin R, Sauter D, Newman T, et al. Continuous versus intermittent albuterol nebulization in the treatment of acute asthma. Ann Emerg Med 1993; 22:1847–1853.
29. Rudnitsky G, Eberlein R, Schoffstall J, et al. Comparison of intermittent and continuously nebulized albuterol for treatment of asthma in an urban emergency department. Ann Emerg Med 1993; 22:1842–1846.
30. Bodenhamer J, Bergstrom R, Drown D, et al. Frequently nebulized beta-agonists for asthma: Effects on serum electrolytes. Ann Emerg Med 1992; 21:1337–1342.
31. Haalboom J, Deenstra M, Struyvenberg A. Hypokalemia induced by inhalation of fenoterol. Lancet 1985; 1:1125–1127.

32. Bohn D, Kalloghlian A, Jenkins J, et al. Intravenous salbutamol in the treatment of status asthmaticus in children. Crit Care Med 1984; 12:892–895.
33. Kurland G, Williams J, Lewiston N. Fatal myocardial toxicity during continuous infusion intravenous isoproterenol during therapy of asthma. J Allergy Clin Immunol 1979; 63:107–111.
34. British Thoracic Society. Guidelines for management of asthma in adults. II: Acute severe asthma. BMJ 1990; 301:797–800.
35. Verbeek P, Gareau A, Rubes C. Treatment of asthma-related respiratory arrest with endotracheal albuterol. Ann Emerg Med 1988; 17:358–360.
36. Rebuck A, Chapman K, Abboud R, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airway disease in the emergency room. Am J Med 1987; 82:59–64.
37. Ward M, Macfarlane J, Davies D. A place for iprotropium bromide in the treatment of severe acute asthma. Br J Dis Chest 1985; 79:374–378.
38. Slovis C, Daniels G, Wharton D. Intravenous use of glycopyrrolate in acute respiratory distress due to bronchospastic pulmonary disease. Ann Emerg Med 1987; 16:898–900.
39. Bramen S, Kaemmerien J. Intensive care of status asthmaticus. JAMA 1990; 264:366–368.
40. Fanta C, Rossing T, McFadden E. Treatment of acute asthma, is combination therapy with sympathomimetics and methylxanthines indicated? Am J Med 1986; 80:5–10.
41. Murphy D, McDermott M, Rydman R, et al. Aminophylline in the treatment of acute asthma when beta$_2$-adrenergics and steroids are provided. Arch Intern Med 1993; 153:1784–1788.
42. Wrenn K, Slovis C, Murphy F, Greenberg R. Aminophylline therapy for acute bronchospastic disease in the emergency room. Ann Intern Med 1991; 115:241–247.
43. Nassif E, Weinberger M, Thompson R, Huntley W. The value of maintenance theophylline in steroid-dependent asthma. N Engl J Med 1981; 304:71–75.
44. Pauwels R. New aspects of the therapeutic potential of theophylline in asthma. J Allergy Clin Immunol 1989; 83:548–553.
45. Milgrom H, Bender B. Current issues in the use of theophylline. Am Rev Respir Dis 1993; 147:S33–S39.
46. McNamara R, Rubin. Intramuscular methylprednisolone acetate for the prevention of relapse in acute asthma. Ann Emerg Med 1993; 22:1829–1835.
47. Larsen G. Asthma in children. N Engl J Med 1992; 326: 1540–1545.
48. Littenberg B, Gluck E. A controlled trial of methylprednisolone in the emergency treatment of acute asthma. N Engl J Med 1986; 314:150–152.
49. Schneider S, Pipher A, Britton H, et al. High dose methylprednisolone as initial therapy in patients with acute bronchospasm. J Asthma 1988; 25:189–193.
50. McNamara R, Spivey W, Skibeloff E, et al. Intravenous magnesium sulphate in the management of acute respiratory failure complicating asthma. Ann Emerg Med 1989; 18:197–199.
51. Leber M, Rao S. Magnesium sulfate used as an adjunct to beta-agonists in acute asthma: A case report. J Emerg Med 1991; 9:377.
52. Kuitert L, Kletchko S. Intravenous magnesium sulfate in acute, life-threatening asthma. Ann Emerg Med 1991; 20:1243–1245.
53. Bloch H, Silverman R, Mancherje N, et al. Intravenous magnesium sulfate as an adjunct in the treatment of acute asthma. Chest 1995; 107:1576–1581.
54. Spivey W, Skobeloff E, Levin R. Effect of magnesium chloride in rabbit bronchial smooth muscle. Ann Emerg Med 1990; 19:1107–1112.
55. Noppen M, Vanmaele L, Nicole I, Schandevyl W. Bronchodilating effect of intravenous magnesium sulfate in acute severe bronchial asthma. Chest 1990; 97:373–375.
56. Skobeloff E, Spivey W, McNamara R, et al. Intravenous magnesium sulfate for the treatment of asthma in the emergency department. JAMA 1989; 262:1210–1213.
57. Pabon H, Moness G, Kissoon N. Safety and efficacy of magnesium sulfate infusion in children with status asthmaticus. Pediatr Emerg Care 1994; 10:200–204.
58. Green S, Rothrock S. Intravenous magnesium for acute asthma: Failure to decrease emergency treatment duration or need for hospitalization. Ann Emerg Med 1992; 21:260–265.
59. Chande V, Skoner D. A trial of nebulized magnesium sulfate to reverse bronchospasm in asthmatic patients. Ann Emerg Med 1992; 21:1111–1115.
60. Betts E, Parkin C. Use of ketamine in an asthmatic child. Anesth Analg 1971; 50:420–421.
61. Fisher M. Ketamine for status asthmaticus. Anesthesia 1977; 32:771–772.
62. Sarma V. Ketamine and asthma. Acta Scand 1992; 36: 1507–1510.
63. Green S, Johnson N. Ketamine sedation for pediatric procedures. Part 2: Review and implications. Ann Emerg Med 1990; 19:1033–1046.
64. L'Hommedieu C, Arens J. The use of ketamine for the emergency intubation of patients with status asthmaticus. Ann Emerg Med 1987; 16:568–571.
65. Rock M, De La Rocha R, L'Hommedieu C, Truemper E. Use of ketamine in asthmatic children to treat respiratory failure refractory to conventional therapy. Crit Care Med 1986; 14:514–516.
66. Hemmingsen C, Kielsen P, Ordorico J. Ketamine in the treatment of bronchospasm during mechanical ventilation. Am J Emerg Med 1994; 12:417–420.
67. Schwartz SJ. Treatment of status asthmaticus with halothane. JAMA 1984; 251:2688–2689.
68. Parnass S, Feld J, Chamberlin W, Segil L. Status asthmaticus treated with isoflurane and enflurane. Anesth Analg 1987; 66:193–195.
69. Bierman M, Brown M, Muren O, et al. Prolonged isoflurane anesthesia in status asthmaticus. Crit Care Med 1986; 14:832–833.
70. Robertson C, Steedman, Sinclair C, et al. Use of ether in life-threatening acute severe asthma. Lancet 1985; Jan 26:187–188.
71. Gluck E, Onarato D, Castriotta R. Helium-oxygen mixtures in intubated patients with status asthmaticus and respiratory acidosis. Chest 1990; 98:693–698.
72. Hall J, Wood L. Management of the critically ill asthmatic patient. Med Clin North Am 1990; 74:779–796.
73. Mountain R, Sahn S. Clinical features and outcome in patients with acute asthma presenting with hypercapnia. Am Rev Respir Dis 1988; 138:535–539.
74. Wiener C. Ventilatory management of respiratory failure in asthma. JAMA 1993; 269:2128–2131.

75. Tuxen D. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis 1989; 140:5–9.
76. Tobin M. Mechanical ventilation. N Engl J Med 1994; 330: 1056–1060.
77. Calhoun W. Management of respiratory failure. Chest 1992; 101(suppl):410S–414S.
78. Manitove SM, Goldring RM. Combined ventilator and HCO_3 strategy in the management of Status Asthmaticus. Am J Med 1983; 74:898–910.
79. Luksza A, Smith P, Coakley J, Gordan I, Atherton S. Acute severe asthma treated by mechanical ventilation: 10 years' experience from a general hospital. Thorax 1986; 41:459–463.
80. MacIntyre N, Silver R, Miller C, et al. Aerosol delivery in intubated, mechanically ventilated patients. Crit Care Med 1985; 13:81–84.
81. O'Doherty M, Thomas S, Page C, et al. Delivery of a nebulized aerosol to a lung model during mechanical ventilation. Am Rev Respir Dis 1992; 146:383–388.
82. Gay P, Rodarte J, Tayyab M, Hubmayr R. Evaluation of bronchodilator responsiveness in mechanically ventilated patients. Am Rev Respir Dis 1987; 136:880–885.

Poisoning and Overdose

DIANE F. GIORGI, M.D.,[1] AND ANDY JAGODA, M.D.[2]

Abstract

The differential diagnosis of all patients with altered mental status must include drug toxicity. In particular, intentional or unintentional overdosing and/or poisoning are common emergency department presenting complaints. A comprehensive approach to managing these patients must incorporate aggressive information gathering, a careful physical examination looking for toxic syndromes, and diagnostic testing. Proper decontamination is the key to effective management, as is the use of specific antidotes when indicated. **Key Words:** poisoning, overdose, toxidromes, gastric lavage, antidotes.

IT HAS BEEN STATED that the magnitude of toxicologic emergencies and the consequent cost to society may in fact constitute a public health crisis (1). Poison Centers have become an established resource for identifying and managing poisonings and might well be the only source of information available regarding a new medication or illicit drug. Poison Centers are regionalized and usually provide 24-hour consultation service; their telephone numbers are readily available through telephone information services or emergency departments. In 1995 there were more than 2.4 million reports of human exposure to toxins that resulted in consultations with a poison center (2). Of these calls, 87% involved accidental overdose, whereas 11% of reported incidents had a suicidal intent. The exact number of persons who present to emergency departments (ED) because of drug overdose is difficult to ascertain. In one hospital, for example, overdoses and other drug-related emergencies were responsible for 38% of visits to the ED (3).

The emergency physician must be able to identify the seriousness of toxic exposures, establish proper patient priorities, and institute decontamination and therapy in a timely fashion. The complex clinical nature of these patients and the diverse toxic substances to which patients may be exposed requires a systematic approach to their evaluation and treatment (4).

Stabilization

Attention to the patient's clinical status is the primary concern during the initial stabilization of the patient with an overdose, whereas, at the same time, the pharmacology of the drug ingested must be taken into consideration. Early consultation with a regional poison control center is indispensable when dealing with an unfamiliar drug. The highest priorities in the management of patients with overdoses are securing the airway and ensuring cardiopulmonary function. The clinical status of some patients with overdoses may change rapidly, as may be seen in the case of a lethal dysrhythmia after a tricyclic overdose or a mixed narcotic overdose resulting in respiratory depression. Vital signs must be recorded frequently and accurately. An accurate temperature is essential for proper treatment because either hyperthermia or hypothermia may complicate the treatment of the patient with an overdose. Oxygen should be administered to all patients with altered mental status or respiratory distress. All delirious, stuporous, or comatose patients, and all patients with unknown ingestions who are at risk of deteriorating, require rapid establishment of intravenous access, and continuous electrocardiogram (ECG) and pulse oximeter monitoring. Cau-

---

From the Department of Emergency Medicine, Mount Sinai School of Medicine, New York. [1]Instructor in Emergency Medicine; [2]FACEP, Associate Professor of Emergency Medicine. Address correspondence to Diane F. Giorgi, M.D., Department of Emergency Medicine, Box 1149, Mount Sinai School of Medicine, New York, NY 10029.

tion should be exercised, however, in relying solely on pulse oximetry to assess the patient's respiratory status (5). The pulse oximeter continuously measures both the pulse rate and the percent oxygen saturation of hemoglobin. The interpretation of the values for oxygen saturation may be limited when peripheral perfusion is impaired. Falsely elevated readings are obtained in the presence of fetal hemoglobin or carboxyhemoglobin, whereas methemoglobin falsely lowers them. Pulse oximetry gives no indication of the extent of hypercarbia as seen in the patient who is hypoventilating or has chronic obstructive pulmonary disease (COPD). Moreover, it does not assess the cellular ability to utilize oxygen as in the case of cyanide poisoning.

Patients with altered mental status require an immediate determination regarding the administration of oxygen, glucose, thiamine, and naloxone (6). Stratification of patients with altered mental status allows the rational decision analysis and may be preferred to giving empiric glucose. Intravenous glucose is recommended when rapid bedside testing is not available, and in patients with altered mental status who have a serum glucose level that is less than 80 mg/dL. Any potential risk of a hyperosmotic load from the glucose exacerbating an intracranial process is outweighed by the benefit of treating an underlying hypoglycemia (6). Thiamine is recommended for all patients who may be malnourished and to whom glucose is administered.

Naloxone (Narcan) is recommended in the dose of 2 mg given intravenously. If the clinical assessment of the patient suggests opiate toxicity or if a history of ingesting a synthetic opiate such as propoxyphene (Darvon) or diphenoxylate (Lomotil) is obtained, and the patient does not respond to the initial dose, doses up to 10 mg may be necessary. Naloxone has a half-life of 1 hour; consequently, patients who overdose with long-acting narcotics are at risk of relapsing after reversal with naloxone. In cases of relapsing symptoms, a naloxone infusion, or administration of nalmefene (Revex), an opioid antagonist with an 8- to 10-hour half-life, beginning with a dose of 0.5 to 1 mg, may be advantageous (7).

Flumazenil (Romazicon) is a pharmacologic antagonist of the central nervous system (CNS) effects of the benzodiazepines. It acts by binding CNS benzodiazepine receptors and competitively blocking benzodiazepine activation of inhibitory γ-aminobutyric acid synapses. In the setting of isolated benzodiazepine overdose, flumazenil is capable of completely reversing coma within 1 to 2 minutes; the therapeutic effect lasts between 1 and 5 hours. Flumazenil is given initially in a dose of 0.2 mg intravenously over 30 seconds. Repeat doses of 0.3 to 0.5 mg over 30 seconds can be given every 30 to 60 seconds up to a total dose of 3 mg until a response is seen (8). Use of flumazenil may result in withdrawal seizures in the chronic abuser of benzodiazepines, or in breakthrough seizures secondary to the antagonism of the anticonvulsant properties of the benzodiazepines in patients with an underlying seizure disorder. It also is contraindicated in patients who have overdosed on drugs such as the tricyclic antidepressants which lower the seizure threshold. Cardiac dysrhythmias have been reported after flumazenil administration in patients with multiple drug overdoses, possibly because of the antagonism of the sympatholytic effects of benzodiazepines (8). Caution must be exercised before administering flumazenil in the overdosed patient and empiric administration is discouraged.

Seizures complicate the stabilization of many drug overdoses (9). The initial management of the intoxicated patient with seizures is similar to that of seizures of other etiologies, although those caused by intoxication may be more difficult to control. Benzodiazepines are the first line of treatment, after which the specific etiology of the seizure must be taken into consideration.

Two circumstances in which seizure activity might be particularly resistant to treatment are isoniazid and methylxanthine overdoses (9). A high index of suspicion is necessary and a good history is crucial to uncovering the facts. Knowing whether the patient or a family member suffers from asthma is important, especially if the presentation includes nausea, vomiting, tremors or abdominal pain before the seizures, or concomitant tachydysrhythmias. The methylxanthines are absorbed rapidly, and peak levels are usually attained 1 to 2 hours postingestion. However, in sustained-release preparation ingestions, the peak levels of theophylline may be delayed for up to 24 hours. Seizures secondary to theophylline toxicity are notoriously recalcitrant to benzodiazepine and phenytoin therapy, and may necessitate the use of phenobarbital or dialysis. The decision to rapidly remove methylxanthine from the intravascular compartment via extracorporeal means depends on the patient's hemodynamic stability.

In isoniazid overdose, the treatment consists of pyridoxine, Vitamin B6, administered intravenously in a gram-for-gram dose. If the dose of isoniazid ingested is unknown, 5 g of pyridoxine is given empirically and repeated in 20 minutes. With the resurgence of tuberculosis, it is important to bear in mind the possibility of an isoniazid overdose, especially in the homeless, those with HIV infection, recent immigrants, or others at high risk for tuberculosis and their family members (10).

History and Physical Examination

Once the patient is stabilized, a focused history is necessary to develop a working diagnosis and initiate a treatment plan. Attention should be paid to the mode of exposure (inhaled, ingested, skin contact), the form of toxic substance (gas, liquid, powder), preparation type (enteric coated, slow release), the quantity, the time of exposure, and the circumstances under which it occurred (accidental or intentional, single or multiple).

A history taken from the patient is often unreliable. Patients can be confused by the drug's effects, or deliberately misleading about suicide attempts or illicit drug use. Talking to friends, relatives, police, or paramedics who were at the scene may provide valuable information. Obtaining empty pill bottles, reviewing medical records, or investigating the clustering of incidences are all important tools in narrowing down the etiology of an overdose.

Patients with altered mental status should be completely undressed and their belongings checked for medications, illicit drugs or paraphernalia, or clues to occupational exposure. The physical and laboratory evaluation must consider trauma, "body packing/stuffing," metabolic abnormalities, hyperthermia or hypothermia, hypoxemia, endocrinologic abnormalities, structural abnormalities such as tumors or hemorrhages, postictal states and psychiatric disorders.

Major toxic signs on evaluation include respiratory irregularities, blood pressure or pulse abnormalities, CNS changes, gastrointestinal disturbances, temperature abnormalities, cardiac dysrhythmias, and skin findings. The patient's odor can also give clues to the etiology. (See Table 1.)

TABLE 1

Characteristic Odors Associated with Specific Overdoses

Burnt almonds	Cyanide
Pears	Chloral hydrate
Moth balls	Camphor
Oil of wintergreen	Methyl salicylate
Fruity	Acetone
Garlic	Arsenic
Vinyl	Ethylchlorovinyl (Placidyl)
Alcohols	Ethanol, isopropyl alcohol
Shoe polish	Nitrobenzene
Rotten eggs	Hydrogen sulfide, disulfiram

Toxidromes

Toxidromes are defined as groups of signs and symptoms that tend to occur consistently with particular toxins. They can be useful in guiding the physician to the type of toxin and to definitive therapies.

Anticholinergic Toxidrome

The peripheral signs of the anticholinergic toxidrome include tachycardia, dry flushed skin, dilated pupils, myoclonus, slightly elevated temperature, urinary retention, and decreased bowel sounds. Central effects include agitation, delirium, seizures, and coma. Morbidity may result from neurologic causes or cardiovascular collapse. The syndrome can be remembered by the mnemonic: hot as a hare, blind as a bat, dry as a bone, red as a beet, mad as a hatter. Antihistamines, antiparkinson medication, atropine, scopolamine, amantadine, antipsychotic agents, antidepressant agents, antispasmodic agents, mydriatic agents, skeletal muscle relaxants, and many plants (notably Jimsonweed and *Amanita muscaria*) can be responsible for this toxidrome.

Sympathomimetic Toxidrome

Delusions, paranoia, tachycardia (or bradycardia if the drug is a pure α-adrenergic agonist), hypertension, hyperpyrexia, diaphoresis, piloerection, mydriasis, and hyperreflexia can be seen with ingestion of sympathomimetics. Seizures, hypotension, and dysrhythmias may occur in severe cases. It may be difficult to distinguish this syndrome from the anticholinergic toxidrome. Hyperactive bowel sounds, diaphoresis, and absence of urinary retention are indicative of a sympathomimetic overdose, whereas dry skin, urinary retention, and absent bowel sounds are more consistent with anticholinergics. Hypertension, although seen more often in sympathomimetic overdoses, may also be present in the anticholinergic syndrome. Cocaine, amphetamine, methamphetamine (and its derivatives), and over-the-counter decongestants (phenylpropanolamine, ephedrine, and pseudoephedrine) have all been implicated in the toxidrome. In caffeine and theophylline overdoses, similar findings, except for the organic psychiatric signs, result from catecholamine release.

Opiate Toxidrome

The person abusing opiates may present with hypotension, respiratory depression, bradycardia, hypothermia, or altered mental status ranging from lethargy to coma. Pupil size is small, bowel sounds are usually decreased, as are reflexes. Seizures may result after overdose of certain opiates such as propoxyphene or meperidine (usually in the pediatric population), or may occur secondary to hypoxia, trauma, hypoglycemia, or a mixed ingestion of an opiate and a drug from another pharmacologic class. Noncardiogenic pulmonary edema, although rare, may also occur. Examining the patient for the presence of needle tracks is helpful, and reversal with naloxone is virtually diagnostic.

Cholinergic Toxidromes

Organophosphate and carbamate insecticides are frequent causes of the cholinergic toxidrome because of their effects at muscarinic, nicotinic, and CNS sites. CNS manifestations include confusion, restlessness, CNS depression, tremors, delirium, coma, and seizures. Miosis (occasionally mydriasis), tachycardia, hypertension, and muscle fasciculations or cramping are all consequences of the nicotinic effects. "SLUDGE" is a mnemonic which refers to the muscarinic component of the toxidrome: Salivation, Lacrimation, Urination, Defecation, Gastrointestinal distress, Emesis. Other muscarinic effects include miosis, bronchorrhea, and bronchoconstriction.

Laboratory Testing

The ordering of laboratory tests should be neither random nor all-encompassing but tailored to the specific situation. The routine use of toxicologic drug screens in the evaluation and treatment of most patients is not recommended (4). The general "toxicology screen" which usually contains common drugs of abuse, is time consuming, expensive, often only qualitative, and rarely alters treatment of the patient (11, 12). When ordering a toxicologic screen it is necessary to know what is included and whether it is a qualitative or quantitative analysis. It is important to remember that screens vary in their sensitivity and that they will not necessarily detect acute ingestions. Consequently, a negative screen does not "rule-out" a toxic ingestion, nor does a positive screen necessarily "rule-in" an acute ingestion. In our institution, for example, a urine toxicology screen analyzes for methadone, opiates, cocaine, barbiturates, amphetamines, benzodiazepines, and phencyclidine. The serum toxicology screen includes analysis for benzodiazepines, barbiturates, tricyclic antidepressants, and ethanol.

In general, it is best not to delay treatment while waiting for the laboratory to confirm toxins. Effective treatment may be initiated after tentative identification of the toxic substance by history and physical examination in the absence of results of toxicologic tests. The physiologic status of the patient must be established and monitored. Supportive care combined with removal or elimination of the toxic substance is sufficient to successfully manage the majority of overdoses (4). Specific antidotal treatments must be based on the patient's physiologic condition and the physician's knowledge about the suspected or known toxic substances.

In certain patients, quantitative toxicologic analysis can be critical. Known or suspected intoxication with salicylates, acetaminophen, iron, methanol, ethylene glycol, carbon monoxide, theophylline, lithium, and digoxin are all indications for quantitative serum testing. Because of the ubiquitous presence of acetaminophen, a level obtained at 4 hours postingestion is recommended in all intentionally poisoned patients. Acetaminophen levels drawn before 4 hours cannot be interpreted accurately because absorption and distribution may not be complete (13).

Serum values of glucose, electrolytes, urea nitrogen, creatinine, acetone, as well as an arterial blood gas and a serum osmolality, are important to assess the metabolic status of the patient. Prothrombin time, partial thromboplastin time, liver function tests, serum alcohol, methemoglobin, or carboxyhemoglobin are recommended in select cases depending on clinical suspicion. Calculation of the anion gap (serum sodium − (chloride + bicarbonate content), may indicate the presence of anions that are not routinely measured and thus help to direct further diagnostic testing. (See Table 2.)

The osmolar gap is the difference between the measured serum osmolarity and the calcu-

TABLE 2
Causes of an Elevated Anion Gap

C = Carbon tetrachloride, cyanide (thiocyanate)
M = Methanol
U = Uremia
D = Diabetes
P = Paraldehyde, phenformin
I = Iron, isoniazid
L = Lactate
E = Ethylene glycol
S = Salicylates, starvation, solvents

lated osmolarity (2 × Na + BUN/2.8 + glucose/18). Normal serum osmolarity is 281 to 289 mOsm/L. A gap of more than 10 suggests poisoning by one of the alcohols and should lead to the ordering of quantitative assays for methanol and ethylene glycol when the gap is not explained by ethanol use or when found in the context of a metabolic acidosis. However, methanol and ethylene glycol may produce a range of acid-base abnormalities depending on the time of ingestion and the time of presentation. Ethylene glycol, and its first metabolite, glycolaldehyde, and methanol, and its first metabolite, formaldehyde, are both osmotically active but do not cause significant acidosis. Their subsequent metabolites, glycolic acid and formic acid, respectively, produce acidosis and an elevated anion gap as the osmolar gap wanes (14). The presence of oxalate crystals in the urine is another important finding that can suggest ethylene glycol ingestion. Isopropanol, typically found in rubbing alcohol, is metabolized to acetone (15). Isopropanol produces no toxic acids as metabolites and will cause an elevated osmolar gap without a concomitant anion gap acidosis (14). The toxicity of isopropanol is caused by its marked sedative effect, approximately twice that of ethanol, with respiratory depression.

An ECG should be obtained to look for dysrhythmias or conduction delays. A tricyclic overdose may cause tachydysrhythmias, or widening of the QRS which is diagnostic of a toxic ingestion (16). Drugs with anticholinergic or sympathomimetic properties can result in nonparoxysmal tachycardias, ventricular tachycardia, or fibrillation. Beta blockers and calcium channel blockers may cause bradycardias and conduction delays. Digitalis overdose may cause conduction abnormalities and atrial or ventricular dysrhythmias.

Radiographs may be useful in identifying radiopaque drug ingestions. "CHIPES" is a mnemonic that is helpful in remembering drugs that might be detected on plain film radiography: Chloral hydrate, Heavy metals, Iodine and Phenothiazines, Enteric coated medication, Sodium chloride tablets.

Management

After initial stabilization, treatment focuses on removal of the toxin to prevent further absorption and toxicity. Initial treatment of dermal or inhalation exposure begins by moving the patient from the toxic environment and removing contaminated clothing. Copious irrigation of eyes and skin is usually the best initial decontamination measure. At times, as with organophosphate pesticide exposures, soap or clorinated solutions may be preferred. Health care workers must ensure their own safety and that of others by preventing further exposures to toxic substances during the care of these patients. Surface barriers, filters, masks, contained-breathing devices, and ocular protective devices must be used as indicated during the decontamination process. Appropriate disposal of contaminated equipment and supplies must be enforced.

Gastrointestinal Decontamination

Gastrointestinal (GI) decontamination of ingested toxins is very controversial. Specific contraindications exist when the risk of pulmonary aspiration of gastric contents is more dangerous than the ingestion. This is true in the case of low viscosity, petroleum-based hydrocarbon ingestions, which can cause significant morbidity and mortality if aspirated. Ingestion of caustic substances, where risk of perforation of the esophagus or stomach exists, is another case in which the induction of vomiting or lavage are contraindicated.

The four principal methods of GI decontamination are syrup of ipecac, orogastric lavage, activated charcoal, and whole bowel irrigation.

Syrup of Ipecac. Ipecac is the extract of "Brazil root" which acts on the chemoreceptor trigger zone. Emesis is usually produced within 20 to 30 minutes of ingestion, and the inability to tolerate fluids may last up to 6 hours. Its efficacy is similar to orogastric lavage if used within 1 hour of ingestion, effecting approximately 30% of drug removal (17, 18). Syrup of ipecac is contraindicated in patients with altered mental status, in children less than 6 months old, in the case of caustic ingestions, and in patients at risk for rapid clinical deterioration. Whenever decontamination with activated charcoal is desired, vomiting will delay administration of the charcoal. Accordingly, syrup of ipecac may still have a useful role in treatment at home, but is of little value in the ED (19).

Orogastric Lavage. This modality of decontamination is also of unproven benefit for routine use. It is best reserved for patients who arrive at the hospital within 1 hour of a toxic ingestion, unless contraindicated (3). A 40 French (or largest allowable tube for the patient's age) orogastric tube is recommended. A gag reflex must be present in the patient with an unprotected airway, otherwise the patient should be intubated. The patient is placed in the left lateral decubitus position and 250-cc aliquots of lavage solution are instilled in adults and then withdrawn at consecutive intervals until the lavage fluid is clear. The administration of activated charcoal before the first aliquot of lavage fluid is of theoretical benefit in preventing absorption of highly toxic adsorbable substances.

Activated Charcoal. Activated charcoal acts by binding the ingested substance in the GI tract, decreasing its absorption and local GI irritation, and removing the toxin systemically by GI dialysis via the enterohepatic circulation (20). It adsorbs most commonly ingested drugs and chemicals and, when indicated, should be administered to patients with overdoses as quickly as possible. It is contraindicated in hydrocarbon and caustic ingestions because it can cause vomiting with potential aspiration, and is ineffective with heavy metals including iron, lithium, and potassium. Most toxins that are bound by activated charcoal require a 10:1 charcoal-to-toxin ratio. The ideal dose is 10 times the weight of the toxin, generally 50 g for the adult and 1 g/kg body weight for the child. A frequency of every 3 to 4 hours is recommended for multiple dose therapy. A cathartic such as sorbitol (adult dose: 1–2 g/kg not to exceed 150 g of a 35% solution) is usually added to the first dose of charcoal. Theoretically, a cathartic enhances the elimination of the activated charcoal/toxin complex, thus minimizing the chance for toxins to desorb from the charcoal back into the gut, but this has never been proven to be of clinical benefit (22). Cathartics are contraindicated in the medically debilitated, if bowel sounds are absent, in renal disease, and in the presence of congestive heart failure or severe hypertension. Fluid and electrolyte imbalances secondary to protracted diarrhea have been shown to occur in children but are rare in adults when a single therapeutic dose of cathartic is used (23). Multiple doses of cathartics, however, can cause dehydration and electrolyte imbalances such as severe hypernatremia and hypokalemia, and should be avoided.

Multiple dosing of activated charcoal at regular intervals, appears to be a safe and effective method of sequestering toxins in the GI tract until their eventual excretion in the feces (24). It enhances the elimination of various substances including phenytoin, tricyclic antidepressants, theophylline, phenobarbital, salicylates, and dapsone, as well as that of many sustained release drugs. Maximum prevention of drug absorption is achieved when the charcoal suspension is given as soon as possible after ingestion. However, after an acute overdose, absorption of a toxin may be prolonged up to 24 hours. This may be due to the drug's limited solubility (phenytoin), anticholinergic properties (tricyclics), or decreased gastric emptying (methylsalicylates). Hence, activated charcoal may be useful in adsorbing or preventing further absorption of toxins in select cases even if its administration has been delayed. Repetitive dosing of activated charcoal may enhance further elimination if the drug undergoes enterogastric or enterohepatic recirculation (24).

Whole Bowel Irrigation. Whole bowel irrigation involves the oral administration of large volumes of commercially available, polyethylene glycol electrolyte lavage solution to irrigate the contents of the GI tract (25, 26). This solution was specifically formulated to prevent any net absorption or secretion of fluid or electrolytes during the procedure (27). Whole-bowel irrigation may flush pill fragments through the GI tract, preventing absorption and toxicity (28). Administration of 1–2 L of polyethylene glycol electrolyte (Golytely, Colyte) solution per hour, either orally or through a gastric tube, is recommended for adult patients and children older than 5 years. The procedure usually takes approximately 4 to 6 hours, and the end point occurs when the rectal effluent takes on the same characteristics as the infusate. Whole-bowel irrigation is a successful decontamination procedure in the case of sustained release substances such as theophylline and diltiazem and after the overdose of other toxins not adsorbed by activated charcoal such as lithium and iron. This technique has also been successful in cases of ingestion of cocaine packets by drug dealers (29).

Enhanced Elimination

The rate of elimination of some drugs may be increased by changing the pH of the urine. This is true of salicylates, chlorpropamide, and phenobarbital ingestions in which alkalinization of the urine increases their excretion (30). These drugs are weak acids and in alkaline solution a greater fraction is in the anionic form. The renal tubule is relatively impermeable to many organic anions that are trapped in renal tubular fluid and excreted when the urine pH is neutral or alkaline. Although the excretion of tricyclic antidepressants and phencyclidine might be increased by acidification of the urine, the danger of exacerbating the cardiac and/or CNS toxicity far outweighs any potential benefits.

Dialysis and Hemoperfusion

The indications for dialysis or hemoperfusion include the ingestion of potentially lethal

TABLE 3
Toxins and Specific Antidotes

Toxin	Antidote	Dosage and Comments
Acetaminophen	*N*-Acetylcysteine	Initial dose 140 mg/kg p.o. followed by 17 doses of 70 mg/kg every 4 hr
Anticholinergic agents	Physostigmine	1–2 mg i.v. over 5 min. Use only for severe delirium. May be useful to treat seizures or tachydysrhythmias, but strong clinical evidence is lacking.
Benzodiazepines	Flumazenil	0.2 mg i.v. over 30 sec. If there is no response after 30 sec, give 0.3 mg over 30 sec. If there is no response after 30 sec, give 0.5 mg over 30 sec at 1-min intervals up to a total dose of 3 mg. Should not be given if tricyclic antidepressants or chronic benzodiazepines have been taken by patient.
Beta-blockers	Glucagon	Starting dose 5–10 mg i.v. titrate to response (normalization of vital signs). Maintenance dose of 2–10 mg/hr may be used.
Bromides	Saline diuresis	If the patient is cooperative 1–2 g of sodium chloride should be given hourly by mouth along with copious amounts of water. Otherwise normal saline should be given i.v.
Calcium channel blockers	Calcium chloride	1 g i.v. over 5 min
	Glucagon	See Beta blockers
Carbon monoxide	100% O_2	Shortens the half-life of CO to 40–80 min. Hyperbaric oxygen shortens the half-life of CO to 20 min.
Coumadin	Vitamin K1	25–50 mg i.v. slowly at 1 mg/min. Takes 4–6 hr for effect.
	Fresh frozen plasma	Reserved for serious hemorrhage.
Cyanide	Sodium nitrite	10 mL of a 3% sodium nitrite
	Sodium thiosulfate	50 mL of 25% sodium thiosulfate i.v.
		Adjust doses for children
	Hydroxycobalamin	Not approved in U.S.A.
Digitalis glycosides	Digoxin-specific antibodies	Equimolar to ingestion. One vial binds 0.6 mg digoxin.
Phenothiazines (Extrapyramidal reactions)	Diphenhydramine	50–100 mg
	Cogentin	1–2 mg
Heparin	Protamine sulfate	1 mg per 100 units heparin.
		50 mg maximum dose
Iron	Deferoxamine	Test dose of 90 mg/kg i.m. The test is positive when the urine turns the color of rosé wine. Treatment: 15 mg/kg/H i.v. infusion; max 6 g/day.
Isoniazid	Pyridoxine	gram-per-gram equivalent. If amount ingested is unknown, start with 5 g i.v.
Lead	Dimercaprol	3–5 mg/kg i.m. every 4 hr for 24–48 hr
Mercury	Dimercaprol	Same as lead
Methanol	Ethanol	Loading dose: 10 mL of 10% solution. Maintenance: 1–2 mL/kg/hr 10% EtOH to maintain serum at 100 mg/dL.
	4-Methyl-pyrazole	Not approved in the U.S.A.
Ethylene glycol	Same as methanol	
Nitrites	Methylene blue	1–2 mg/kg/i.v. as a 1% solution, given slowly over 5 min. A second dose can be given after 1 hr.
Opiates	Naloxone	Starting dose 2 mg. More may be needed for overdoses of some synthetic narcotics.
	Nalmefene	0.5 mg/70 kg i.v.
Organophosphates Carbamates	Atropine	Test dose 2 mg i.v. over 5 min. Repeat in larger increments until drying of secretions.
	Praladoxime	2–4 mg i.v. Contraindicated in some carbamate poisonings.
Tricyclic antidepressants	Bicarbonate	1–2 mmol/kg i.v. for QRS widening or ventricular dysrhythmias.

amounts of a dialyzable toxin where the normal route of elimination is impaired and prolonged exposure may potentiate serious organ injury. Hemoperfusion, which is performed by pumping blood through a cartridge containing activated charcoal, is indicated when the ingested substance can not be dialyzed but can be preferentially adsorbed to activated charcoal despite protein binding or increased molecular weight. This modality is effective in the treatment of overdose of drugs such as theophylline, barbiturates, and salicylates.

Dialysis involves the use of a semipermeable membrane to separate diffusible from less or nondiffusible substances. The rate of effective removal of toxic compounds by dialysis and hemoperfusion is affected by the properties of the toxin including its molecular weight, charge, tissue binding, and volume of distribution, as well as the flow rates of blood and dialysate, the properties of the membrane and/or adsorbent. Toxins which are most likely to be cleared by dialysis are those which have a small molecular weight, low protein binding, and a small volume of distribution. These include lithium, methanol, ethylene glycol, salicylates, and theophylline.

Immunotherapy

Heterologous antibodies have been developed for analytic, diagnostic, and therapeutic use. A strategy common to these applications is equimolar neutralization of the antigen, in which the amount of antibody administered is sufficient to bind every molecule of the antigen. Therapeutic uses of antibodies in toxicology include the neutralization of crotalidae venom with antivenin and immunotherapy for hymenoptera stings. The only therapeutic antibody commercially available for the treatment of drug intoxication is digoxin Fab (Digibind) (31). An ovine desipramine-specific Fab antibody fragment has been produced, and its efficacy on the reversal of cardiovascular toxicity in tricyclic overdoses is being studied (32).

Antidotes

Gastric decontamination and supportive care are sufficient to manage most intoxications. However, there are drugs which have specific antidotes which will counter or neutralize the toxin's effects. (See Table 3.)

Conclusion

Aggressive initial stabilization and comprehensive supportive care are essential to limit the effects of toxins on primary organ systems. Patients must be closely monitored with frequent reassessment of vital signs and physical findings as the clinical picture can deteriorate rapidly. Diagnostic studies and therapeutic interventions must be performed based on clinical suspicion of a specific toxin or toxidrome. If there is the potential need for special procedures such as dialysis, contact with the specialists should be made earlier rather than later, even if it is only to inform them of the possibility. The decision to admit or discharge the patient is based on the type of toxin ingested, the amount taken, and the potential for prolonged adverse effects. Psychiatric evaluation should be sought for any suicide attempt even if the patient is being admitted to another service.

References

1. Hoffman RS, Goldfrank LR. The impact of drug abuse and addiction on society. Emerg Med Clin North Am 1990; 8:467–480.
2. Litovitz T, Felberg L, White S, et al. 1995 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System, 1995. Am J Emerg Med 1996; 14:487–494.
3. Kulig K. Initial management of ingestions of toxic substances. N Engl J Med 1992; 326:1677–1681.
4. American College of Emergency Physicians. Clinical policy for the initial approach to patients presenting with acute toxic ingestion or dermal or inhalation exposure. Ann Emerg Med 1995; 25:570–585.
5. American Medical Association. The use of pulse oximetry during conscious sedation. JAMA 1993; 270:1463–1467.
6. Hoffman R, Goldfrank L. The poisoned patient with altered consciousness. JAMA 1995; 274:562–569.
7. Barsan W, Seger D, Danzl D, et al. Duration of antagonistic effects of nalmefene and naloxone in opiate-induced sedation for ED procedures. Am J Emerg Med 1989; 7:155–161.
8. Votey S, Bosse G, Bayer M, Hoffman J. Flumazenil: A new benzodiazepine antagonist. Ann Emerg Med 1991; 20: 181–188.
9. Kunisaki T, Augenstein L. Drug and toxin induced seizures. Emerg Med Clin North Am 1994; 12:1027–1056.
10. Blanchard P, Yao J, McAlpine D, Hurt R. Isoniazid overdose in the Cambodian population of Olmsted County, Minnesota. JAMA 1986; 256:3131–3133.
11. Hepler B, Sutheimer C, Sunshine I. Role of the toxicology laboratory in the treatment of acute poisoning. Med Toxicol 1986; 1:61–70.
12. Brett AS. Implications of discordance between clinical impression and toxicology analysis in drug overdose. Arch Intern Med 1988; 148:437–441.
13. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics 1975; 55:871–876.
14. Trummel J, Ford M, Austin P. Ingestion of an unknown alcohol. Ann Emerg Med 1995; 27:368–374.
15. Natowicz M, Donahue J, Gorman L, et al. Pharmacokinetic analysis of a case of isopropanol intoxication. Clin Chem 1985; 31:326–328.
16. Boehnert M, Lovejoy F. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. N Engl J Med 1985; 313:474–479.
17. Tandberg D, Diven BG, McLeod JW. Ipecac-induced emesis versus gastric lavage. A controlled study in normal adults. Am J Emerg Med 1986; 4:205–209.

18. Tenenbein M, Cohen S, Sitar DS. Efficacy of ipecac-induced emesis, orogastric lavage, and activated charcoal for acute drug overdose. Ann Emerg Med 1987; 16:838–841.
19. Olsen KR. Is gut emptying all washed up? Am J Emerg Med 1990; 8:560–561.
20. Park GD, Spector R, Goldberg MJ, et al. Expanded role of charcoal therapy in the poisoned and overdosed patient. Arch Intern Med 1986; 146:969–973.
21. Olkkola K. Effect of charcoal-drug ratio on antidotal efficacy of oral activated charcoal in man. Br J Clin Pharmacol 1985; 19:767–773.
22. Krenzelok E, Keller R, Stewart R. Gastrointestinal transit times of cathartics combined with charcoal. Ann Emerg Med 1985; 14:1152–1155.
23. Riegel J, Becker C. Use of cathartics in toxic ingestions. Ann Emerg Med 1981; 10:254–258.
24. Jones J, McMullen M, Dougherty J, Cannon L. Repetitive doses of activated charcoal in the treatment of poisoning. Am J Emerg Med 1987; 5:305–311.
25. Tenenbein M, Cohen S, Sitar DS. Whole bowel irrigation as a decontamination procedure after acute drug overdose. Arch Intern Med 1987; 147:905–907.
26. Tenenbein M. Whole bowel irrigation as a gastrointestinal decontamination procedure after acute poisoning. Med Toxicol 1988; 3:77–84.
27. Davis G, Santa Ana C, Morawski S, et al. Development of a lavage solution associated with minimal water and electrolyte absorption or secretion. Gastroenterology 1980; 78:991–995.
28. Burkhart K, Wuerz R, Donovan JW. Whole-bowel irrigation as adjunctive treatment for sustained-release theophylline overdose. Ann Emerg Med 1992; 21:1315–1320.
29. Hoffman RS, Smilkstein MJ, Goldfrank LR. Whole bowel irrigation and the cocaine body packer: A new approach to a common problem. Am J Emerg Med 1990; 8:523–527.
30. Garrettson L, Geller R. Acid and alkaline diuresis: When are they of value in the treatment of poisoning? Drug Safety 1990; 5:220–226.
31. Bayer M. Recognition and management of digitalis intoxication: Implications for emergency medicine. Am J Emerg Med 1991; 9(suppl):29–32.
32. Dart R. Ovine Desipramine antibody fragments reverse desipramine cardiovascular toxicity in the rat. Ann Emerg Med 1996; 27:309–314.

Emergency Airway Management

Paul H. Hamilton, M.D.,[1] and John J. Kang, M.D.[2]

Abstract

Maintenance of the airway is the most important and one of the most challenging functions that an emergency physician has to perform. This article is a review of the various techniques that can be used by both emergency and nonemergency physicians to secure the airway. It includes standard orotracheal intubation, nasotracheal intubation, fiberoptic intubation, and cricothyroidotomy. The medications used in these procedures and in rapid sequence intubation are discussed. **Key Words:** Intubation, airway, emergency, resuscitation, neuromuscular blockade, rapid sequence intubation.

Recognition and appropriate management of the compromised airway is one of the most challenging tasks in the emergency department. In the "ABCs" of emergency patient management, the airway is the primary and immediate concern of the resuscitative effort. The physician is confronted with a myriad of airway emergencies caused by a wide spectrum of disease processes across all age groups. Successful management depends on being knowledgeable about and equipped for multiple techniques of airway management. Success also depends on detailed knowledge of the sedating and paralyzing agents used in these techniques. This article will describe the techniques and medications that are generally used in the emergency department today.

An adequate patent airway allows for proper oxygenation and ventilation of the patient. Those patients who are unable to maintain an adequate airway because of a pathologic obstruction or mental obtundation require intubation. Patients with impaired protective reflexes require intubation to prevent aspiration, and those with refractory hypoxia or profound hypercarbia require intubation to allow mechanical ventilation. Patients requiring therapeutic hyperventilation or controlled hypoventilation are also candidates for intubation. Severely agitated and combative patients, who can not be controlled by conscious sedation and who require diagnostic imaging, should be intubated to permit the degree of pharmacologic restraints needed to facilitate appropriate work-ups. Common indications for intubation are listed in Table 1.

Airway Intubation Techniques

Endotracheal intubation requires cognitive and motor skills that can only be acquired through proper training and must be maintained through regular use or retraining. All providers should become familiar with basic life support techniques; those who predictably encounter patients requiring advanced airway management should be trained in endotracheal intubation.

Before intubating patients, it is important to pretreat them with oxygen and have the appropriate equipment necessary for intubation. (See Table 2.) Ideally, the physician should be competent with both straight and curved blades. The physician should also prepare for complications which may occur with intubation, and must be prepared to institute an alternative technique in case of failure. (See Table 3.) Once intubation has been accomplished, tube placement must be confirmed by auscultation, measurement of end-tidal carbon dioxide level, and chest radiograph.

From the Department of Emergency Medicine, Elmhurst Hospital Center. [1]Associate Attending; [2]Associate Attending. Address correspondence to Paul H. Hamilton, M.D., Elmhurst Hospital Center, Department of Emergency Medicine, 79-01 Broadway, Elmhurst, NY 11373.

TABLE 1
Indications for Intubation

Upper airway obstruction	Trauma, tumor, infection, edema, foreign body, laryngospasm, stenosis
Airway protection	Coma, overdose, stroke, gastric lavage, absent gag reflex, sedation of combative patients
Hypoventilation	Apnea, thoracic trauma, paralysis of respiratory muscles, shock, asthma, COPD, respiratory failure or insufficiency
Hypoxia	Pulmonary edema, congestive heart failure, shock, toxic inhalations, pulmonary infections, sepsis
Treatment of special conditions	Hyperventilation of patients with head trauma or cerebral edema, controlled hypoventilation for asthma

TABLE 2
Equipment for Intubation

Suction with appropriate suction catheters (large bore and flexible)
Pulse oximeter
Cardiac monitor
Oxygen source
Bag valve mask
Ambu-Bag of appropriate tidal volumes
Ventilator
Crash cart with medications
Oral airways
Nasogastric tubes
Laryngoscope with various size blades (straight and curved)
Endotracheal tubes of various sizes
Endotracheal tube stylets
End-tidal carbon dioxide detector
Magill forceps

TABLE 3
Complications of Intubation

Esophageal intubation
Right mainstem intubation
Pharyngeal trauma
Vocal cord trauma
Tracheal perforation
Bleeding
Aspiration
Dislocation of the mandible
Fracture of the epiglottis
Chipping or loosening of the teeth
Neck strain
Dislocation of the unstable cervical spine

Direct Laryngoscopic Orotracheal Intubation

Direct laryngoscopy and orotracheal intubation is the most commonly attempted initial intubation technique. The medications used to facilitate intubation of such patients range from nothing to rapid sequence intubation, where both an induction and paralytic agent are used. Patients who are in extremis often require no medications and may be intubated easily without sedating or paralyzing agents. Rapid sequence intubation (RSI), which is discussed at length below, is usually the method of choice in the emergency department setting. The still common practice of using sedation alone, with an amnestic or narcotic agent, to facilitate intubation in acutely ill patients offers no advantage over RSI. This is best reserved for patients who have a specific contraindication to neuromuscular blockade. Special situations may require that consciousness be maintained during intubation; in these cases awake intubation with local anesthesia is indicated.

Rapid Sequence Intubation

The use of paralytic agents dates back to 1942 when curare was first used for general anesthesia. Since then, shorter acting depolarizing and nondepolarizing agents have been developed. These agents have been used successfully in intubations in the prehospital arena, in the emergency department, in the trauma center, and in the operating room (1–5). In one study the most common uses of RSI were for critically ill patients with head trauma, alcohol or drug intoxication, multiple trauma, cardiac emergency, respiratory insufficiency, and seizures (6). RSI techniques are also practiced by prehospital providers in some jurisdictions (7).

Rapid sequence intubation refers specifically to the use of an induction agent in conjunction with a paralyzing agent to facilitate intubation while minimizing the risk of aspiration. This technique has many advantages in the emergency department where patients who require intubation present with recent food ingestion or an unobtainable history (1). The term originates from the “rapid sequence” or almost simultaneous administration of both the induction and paralytic agents. In addition to these agents, pretreatment medications may be administered to prevent complications associated with the intubation or with specific agents.

Whenever RSI is used the possibility of failure and the need for a surgical airway should always be considered and preparations made. RSI allows for the rapid and controlled intubation of patients, eliminating or minimizing factors which make intubation difficult, and reducing the adverse effects of intubation. The appropriate sequence for RSI is shown in Table 4.

The use of RSI in the pediatric population has been shown to be safe and effective (8, 9). A significant number of intubations in pediatric trauma cases are for head injury, and RSI is indicated to decrease the adverse effects of intubation on intracranial pressure (10). Many patients require RSI in order to be intubated successfully (11). Patients intubated without the use of RSI have been shown to have higher rates of complications and to require more attempts than those intubated with RSI (12). The RSI protocol for the pediatric population should include the use of atropine to prevent the bradycardia associated with vagal stimulation and the hemodynamic compromise that may occur without its usage (13, 14). No formal cutoff age exists for the use of atropine, but general protocols recommend its use for children younger than 4 years of age (13).

Premedications. Both the physical act of intubation and the pharmacologic agents used in RSI have the potential for adverse physiologic effects. Premedications are used to block these physiologic effects. Intubation causes a transient increase in heart rate, blood pressure, intracranial pressure, and intraocular pressure. This response typically lasts 5 minutes or less and is of uncertain clinical significance. Intravenous lidocaine has been recommended to blunt this response and specifically to limit increases in intracranial pressure, although its efficacy for this purpose is controversial. The dose of lidocaine is 1–1.5 mg/kg IV, administered 2 to 3 minutes before intubation.

Succinylcholine is an important part of most RSI protocols. It does have some undesirable effects, most of which are related to the production of muscle fasciculations. Pretreatment with a small "defasciculating dose" of vecuronium, a nondepolarizing neuromuscular blocking agent, will largely prevent the fasciculations and secondary adverse effects. The dose of vecuronium for this purpose is one-tenth of the full paralyzing dose or 0.01 mg/kg IV, 1 to 2 minutes before administration of succinylcholine.

"Minidose" succinylcholine as a pretreatment to prevent muscle fasciculations has also been found to be effective. The dose for this purpose is 0.1 mg/kg IV of succinylcholine 1 to 2 minutes before the paralyzing dose (15).

In infants and children succinylcholine can cause bradycardia. These patients and adults who are bradycardic or receiving multiple doses of succinylcholine should be pretreated with atropine. The dose of atropine is 0.01–0.02 mg/kg IV, up to 0.5 mg. Regardless of the patient's size, never give less than 0.1 mg of atropine because a smaller dose can cause paradoxical bradycardia (16).

TABLE 4

Rapid Sequence Intubation

1. Preparation (equipment, medications, support staff)
2. Preoxygenation (5 min of 100% oxygen via face mask or 3 conscious deep breaths of 100% oxygen if time is lacking)
3. Pretreatment
4. Paralysis
5. Pass the tube under direct visualization

Sedating Agents. A variety of drugs are available to sedate patients before intubation. Selection of the most appropriate sedative or anesthetic depends on the characteristics of the patient involved, the side effect of the drug, and the personal preference and experience of the physician.

Fentanyl is a synthetic narcotic analgesic that is 50 to 100 times more potent than morphine. Fentanyl causes little or no histamine release and therefore rarely causes hypotension. Fentanyl has the added advantage of blunting the pressor response of intubation and also decreases intracranial pressure. These properties make fentanyl a good sedating agent in the patient with head trauma or in patients with increased intracranial pressure. Fentanyl may also lower the cardiovascular stress response of tachycardia, hypertension, and dysrhythmias (17). The dose of fentanyl generally used for RSI is 3–5 μg/kg IV. This produces sedation in about 2 minutes and has a duration of 30 to 40 minutes. At higher doses, fentanyl can cause muscle rigidity which can be abolished by neuromuscular blocking agents. Naloxone can be used to reverse the central and peripheral effects of fentanyl (18–20).

Etomidate is a potent hypnotic agent without analgesic properties. Etomidate has a rapid onset (less than 1 minute), and a duration of action of about 5 minutes (21). It has less effect on hemodynamics than any other sedative-anesthetic agent, and reduces both intracranial and intraocular pressures. These properties make etomidate an excellent sedative for most patients including patients with multiple trauma, head trauma, and increased intracranial pressure, and patients who are in shock. The dose of etomidate is 0.3 mg/kg IV. The main adverse effects of etomidate are myoclonic movements and pain on injection, both of which can be decreased by giving a benzodiazepine or a narcotic. Patients may also experience postanesthesia nausea and vomiting when used in conjunction with opiates. Decreased adrenal steroidogenesis with decreased plasma cortisol levels may occur even with single-dose therapy with etomidate (21).

Ketamine produces a "dissociative anesthesia," in which the patient is awake but is insensate, unresponsive to pain, and completely amnestic. Ketamine increases cardiac output, heart rate, blood pressure, myocardial oxygen consumption, intracranial pressure, and intraocular pressure. This makes ketamine a good sedating agent in the hypotensive patient with good cardiac function. The most useful side effect of ketamine is that it is a potent bronchodilator. It is the sedative of choice in an otherwise healthy asthmatic. The most notorious side effect of ketamine is the emergence reaction, which consists of hallucinations, dysphoria, or both, and occurs as the patient emerges from sedation. These reactions are less common in the pediatric population (14). Both benzodiazepines and narcotics effectively suppress the emergence phenomena. The dose of ketamine for RSI is 1–2 mg/kg IV with onset of action in less than 1 minute and duration of 5 to 10 minutes (22).

Midazolam (Versed®) is a water-soluble benzodiazepine that has a rapid onset (1–2 minutes) and short duration of action (20 minutes). It has anticonvulsant, muscle relaxant, and amnestic properties. Midazolam does not increase intracranial pressure, making it safe for use in the patient with head trauma or the patient with increased intracranial pressure. Midazolam may decrease systemic vascular resistance and thereby cause a slight decrease in blood pressure and increase in heart rate. The dose of midazolam for RSI is 0.02–0.1 mg/kg IV.

Thiopental is an ultra-short-acting barbiturate (lasting 5 to 10 minutes) with a rapid onset (<1 min). Thiopental has a special place in the intubation of the patient with head injuries because it not only blocks the pressor response but also reduces cerebral metabolism and intracranial pressure. Thiopental administration may cause hypotension due to vasodilation and myocardial depression and thus should be avoided in hypotensive or hypovolemic patients. Thiopental may also cause laryngospasm and bronchospasm and thus should be avoided in patients with asthma and porphyria. The dose of thiopental in RSI is 2–5 mg/kg IV.

Methohexital is similar to thiopental except that its duration of action is shorter, lasting approximately 5 minutes. Methohexital has a higher incidence of muscle spasm than thiopental. The dose of methohexital in RSI is 1 mg/kg.

Paralytic Agents. *Succinylcholine* is a depolarizing neuromuscular blocking agent with a rapid onset (<1 minute) and short duration (5 minutes). In studies comparing succinylcholine with other paralytics, succinylcholine was found to have the fastest onset of action (23). Although it is the most common muscle relaxant used in RSI, it has several disadvantages. It may cause increases in intracranial, intraocular, and intragastric pressures but its use is not contraindicated in the patient with acute head injuries (14). Other undesirable effects of succinylcholine include muscle fasciculations, which can be avoided by pretreatment with a defasciculating dose of a nondepolarizing muscle relaxant or of succinylcholine (15), malignant hyperthermia, hyperkalemia, hypertension, and dysrhythmias. Avoid succinylcholine in patients with neuromuscular diseases and with crush injuries, as well as in patients more than 1 week after burns or trauma. The dose of succinylcholine in RSI is 1 mg/kg IV in adults, 1.5 mg/kg IV in adults who were given a defasciculating premedication, and 2 mg/kg in children younger than 10 years of age.

Pancuronium is a nondepolarizing neuromuscular blocking agent with an onset of action of 2 to 3 minutes and duration of action of 60 minutes. Pancuronium is used when prolonged paralysis is needed. It frequently increases heart rate and causes histamine release. The dose of pancuronium is 0.1 mg/kg IV.

Vecuronium is the most frequently used nondepolarizing neuromuscular blocking agent. It has an onset of action of 2 to 3 minutes, but its duration of action is only 30 minutes and does not cause significant histamine release or tachycardia. Studies using high-dose vecuronium, 0.3 mg/kg IV, have only succeeded in prolonging the effect of the paralysis without decreasing the onset of action (24, 25). The dose of vecuronium is 0.1 mg/kg IV.

Atracurium is similar to vecuronium but is the preferred agent in patients with renal or hepatic insufficiency. It occasionally causes histamine release and hypotension. The dose of atracurium is 0.5 mg/kg IV, and its duration of action is 20 to 30 minutes.

Rocuronium bromide is a reversible nondepolarizing neuromuscular blocking agent which is structurally different from vecuronium in four positions (23). It was designed to be an alternative to succinylcholine, providing as short an onset of action as succinylcholine, but without the adverse effects reported with succinylcholine. Rocuronium is 5 to 10 times less potent than vecuronium but has a shorter onset of action (26–28). Studies have shown that rocuronium provides intubating conditions as good as succinylcholine (29, 30). Succinylcholine however still was found to have shorter onset times and a shorter duration of action when compared with rocuronium (31, 32). Similar onset of action times were only achieved by giving higher doses of rocuronium, which caused even longer duration of action when compared with succinylcholine (33). Rocuronium also has a longer duration of action in elderly patients (34).

The dose of rocuronium ranges from 0.5–1.0 mg/kg (29, 35). The higher the dosage, the shorter the onset of action, but the longer the duration of action. In one study the onset times varied from 135 to 271 seconds and the duration of action from 27 to 53 minutes, depending on the dosage (36). Some studies have reported rocuronium to have even shorter onset of action, as low as 89 seconds (29). Rocuronium may be used as an alternative to succinylcholine, but the duration of action is prolonged at higher doses.

Awake Orotracheal Intubation

An awake oral intubation is considered when a patient requiring intubation has either pathologic or anatomic factors which may result in collapse of the airway if neuromuscular blockade is used (37). This technique involves the use of local anesthetics and sedating agents which will facilitate the intubation of the "awake" patient. A common example is the trauma patient with a stab wound or gun-shot wound to the neck. In this situation, bleeding or an expanding hematoma can lead to a compromised airway. Use of paralytics in these situations may cause loss of the patient's muscle tone and complete obstruction of the airway (38). An awake intubation allows the patient to be "awake" enough to maintain their own airway and minimize this occurrence.

The combination of sedating agents and liberal airway anesthesia, which allows for direct visualization of the airway and orotracheal intubation, is the hallmark of this technique. These patients are sedated just enough to minimize discomfort while allowing patient feedback and maintenance of normal patent airway musculature. Topical and local anesthesia are used to anesthetize the airway to prevent gagging and discomfort. Several different methods of topical anesthesia are available. These patients may initially be given local anesthesia of the posterior tongue, palate, uvula tonsillar pillars, and the posterior pharynx with lidocaine or cetacaine aerosol spray. Another method in cooperative patients is for them to gargle with 30 cc of 2–4% lidocaine solution (39). Nebulized lidocaine has also been used with 4 cc of 4% lidocaine solution via a mask to anesthetize the oral cavity, pharynx, larynx, and trachea (39). Some add 0.5% neosynephrine to the nebulization. Nerve blocks of the lingual branch of the glossopharyngeal, and the internal branch of the superior laryngeal nerve are another alternative (37, 39). Anesthesia of the larynx can be performed by injecting lidocaine over the cricothyroid membrane and injecting 2 cc of 4% lidocaine into the lumen of the larynx (39). The choice of sedating agents is variable, but the use of fentanyl and midazolam is a good option.

Blind Intubation Techniques

Standard tracheal intubation is usually performed with direct visualization of the passage of the endotracheal tube through the vocal cords. In certain situations, however, the blind or nonvisualized technique may be necessary either because of failure of the standard technique or the special circumstances of the patient. Blind techniques of intubation include the nasotracheal, the manual digital, the blind orotracheal, and the transilluminated technique.

Nasotracheal Intubation

Nasotracheal intubation (NTI) may be considered in patients who have a patent airway and spontaneous respirations; it is used in the intubation of patients with asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure, and trauma. Some studies show that nasotracheal intubation is as successful as endotracheal intubation (40). The major advantage of nasotracheal intubation is that it allows intubation of the awake patient. However, there are several disadvantages to the technique. First, it is performed in a blind fashion, and trauma with epistaxis is a common occurrence. Other complications include increased intracranial pressure, esophageal intubation, emesis by stimulation of the gag reflex and subsequent aspiration, sinusitis, trauma to the airway and vocal cords, retropharyngeal perforation with submucosal dissection and creation of false passages, and bacteremia (41). There are also several contraindications to this technique including midface fractures, basilar skull fractures in which the cribriform plate is disrupted, apnea, combative, obtunded, or inebriated patients (42), and foreign bodies in the upper airway (41).

To minimize the trauma that may occur, a topical vasoconstrictor such as neosynephrine or a topical anesthetic such as lidocaine or cocaine should be used. A nasal airway inserted before intubation may allow for progressive dilation of the nares. Select an endotracheal tube that is one size smaller than that which would be used orally in the patient, and lubricate it liberally. Gently insert the endotracheal tube through the nares into the pharynx. Once the tube is in the pharynx, listen to the airflow. When the airflow is maximal during inspiration, advance the tube into the trachea. Using a flexible tip tube (Endotrol tube®) and neck flexion (when it is not contraindicated) may improve the success of intubation (43).

Blind Orotracheal Intubation

This technique is similar to nasotracheal intubation except the endotracheal tube is passed through the mouth instead of the nose; therefore, one does not need to be concerned about the contraindications associated with nasotracheal intubation. In this technique the head is extended and an assistant provides subluxation and anterior traction of the lower jaw (44). A styletted endotracheal tube with the distal end bent in hockey-stick fashion (approximately 60 to 90 degrees), is passed into the oropharynx and directed toward the trachea. The intubator uses the nondominant hand to perform the Sellick maneuver and feel for the end of the endotracheal tube. If the endotracheal tube does not pass through into the trachea, the intubator moves the larynx toward the side where he or she feels the end of the tube (44). Because of the degree of manipulation of the neck, this technique is contraindicated in the trauma patient with a suspected cervical spine injury.

Manual Digital Intubation

The manual digital intubation technique is a rapid method of intubating patients. The index and middle fingers of the nondominant hand are introduced following the curve of the tongue, and the epiglottis is palpated. The endotracheal tube is then passed from one corner of the mouth, under the epiglottis, as the index finger guides the tube into the trachea. Advantages to this technique are the simplicity, the quickness, and the minimal equipment necessary to perform the intubation. Disadvantages are the high risk of right mainstem intubation and bite injuries to the person performing the technique. It is best performed on the apneic, unconscious, or paralyzed patients (41).

Transilluminated Intubation

Many adjuvants to intubation have been developed, including lighted stylets also known as light wands (e.g., Tube-Stat®, Trachlight®). Although new to the emergency department physician, the transilluminated technique dates back to 1959 (45). These are stylets equipped with a bright light source at the end of the stylet. With anterior traction of the lower jaw, the hockey-stick, lighted stylet is passed into the oropharynx. The piriform sinus may be used as an initial stop to gauge the depth of insertion of the stylet, as it approximates the level of the epiglottis. The stylet is then withdrawn slightly and the stylet is directed toward the midline. The position of the stylet is indicated by the degree of brightness. A bright light indicates position in the trachea and the endotracheal tube may be passed over the stylet and the stylet removed. A dimmed light indicates placement in the piriform sinuses, and a very dimmed light indicates placement in the esophagus (41). The transilluminated technique may be performed nasotracheally as well, although the success rate may be less than that done orotracheally (45). This technique may be advantageous in the patient with fixed dental appliances (46), and in trauma patients in whom cervical injury is a concern (45). Disadvantages include difficultly in patients with a thick neck or distorted neck anatomy and the need for diminished light in the room where the technique is being performed. Because of the need for darkness, the use of transilluminated intubation in the field in broad daylight is precluded. For accurate and successful intubation with this technique familiarity with the equipment and technique is critical (43).

Fiberoptic Intubation

Fiberoptic intubation is a relatively new and uncommonly used technique in the emergency department. Whereas blind airway intubation techniques are used in instances where direct laryngoscopic visualization is impossible, fiberoptic intubation allows direct visualization even when the conditions are most adverse (47). Fiberoptic intubation may be done nasotracheally or orotracheally; the former is more common. Using a flexible bronchoscope, visualization of the vocal cords is accomplished, and the endotracheal tube is passed over the bronchoscope into the trachea.

Although the concept seems fairly straightforward, fiberoptic intubation has several disadvantages. When secretions or blood make visualization of the airway difficult, fiberoptic intubation may be impossible to perform (43). This is one of the most common reasons for failure of the fiberoptic technique (48). Another disadvantage is the amount of time required to perform the procedure (49), and its success depends on the expertise of the performer. It should only be performed by a physician experienced with its technique. The maintenance and cleaning of the bronchoscope is costly and time consuming. Fiberoptic intubation, however, may be useful in situations such as cervical ankylosis and severe angioedema (48). It may actually avoid placement of a surgical airway when one would otherwise be performed.

Retrograde Intubation

When orotracheal or nasotracheal intubations fail, retrograde intubation can be the next technique attempted before advancing to a surgical airway. Specific indications for the use of retrograde intubation include trismus, upper airway masses, ankylosis of the jaw, cervical arthritis, and maxillofacial trauma (37). Contraindications to this procedure include coagulopathies, distortion of the normal neck anatomy secondary to a mass or bleeding, and an inability to open the mouth adequately. The equipment necessary for this procedure includes: Magill forceps, a long guide wire such as those usually found in central line kits, a large-bore needle (12–14 gauge), and a syringe. The Cook® Retrograde Intubation set includes an 18 gauge catheter-needle set, a guide wire, and an obturator guide (50).

The cricothyroid membrane is first identified and a large-bore needle is introduced in the cephalad direction with negative pressure applied using a syringe. Once air is introduced into the syringe from the trachea a guidewire is passed through the needle in the Seldinger fashion toward the oropharynx. The guidewire is identified emerging from the oropharynx and caught with the Magill forceps. The guidewire is then passed through the side port of the endotracheal tube which is fed over the guidewire. It is important to maintain tension on the guidewire to facilitate easy passage of the endotracheal tube into the trachea. Once the endotracheal tube is felt at the puncture site, the guidewire is removed and endotracheal tube is advanced into the trachea. The main disadvantage to the retrograde intubation technique is the amount of time necessary for the procedure.

If time permits, and the patient condition warrants it, local anesthesia of the cricothyroid membrane can be given using lidocaine before performing the puncture (42). Retrograde intubation has been shown to be successful in both trauma and nontrauma patients (41, 51).

Surgical Airway: Cricothyroidotomy

Emergency cricothyroidotomy is an alternative method of establishing an airway when other methods fail or are contraindicated. Other surgical airway techniques should not be performed in the emergency department setting.

Emergency cricothyroidotomy is indicated in patients who have severe facial trauma which renders other techniques impossible, who have an upper airway obstruction, and in whom other methods have failed.

Anatomy

The cricothyroid membrane is a thin membrane approximately 10 mm by 22 mm and lies between the cricoid cartilage inferiorly and the thyroid cartilage superiorly. This can be located by first identifying the Adams apple (laryngeal prominence) and palpating approximately 1 to 1.5 fingerbreadths below it in the midline of the neck. The cricoid cartilage should be easily palpated below the membrane.

When there is significant distortion of the neck anatomy, the cricothyroid membrane can usually be identified by placement of the small finger of the right hand in the patient's suprasternal notch, followed by placement of the ring, long, and index fingers adjacent to this in a stepwise fashion up the neck with each finger touching the one below it. This generally results in the index finger being on or near the cricothyroid membrane.

The superior cricothyroid vessels run transversely across the upper third of the cricothyroid membrane and can be avoided by entering the membrane through its inferior third. The anterior jugular veins run vertically in the lateral aspect of the neck and can be avoided by using a vertical incision (52).

Equipment

Only a few instruments are required for successful completion of a cricothyroidotomy: scalpel (with #11 blade), tracheal hook, Trousseau dila-

TABLE 5

Cricothyroidotomy: Contraindications and Complications

Contraindications to cricothyroidotomy
1. Pediatric age group (<10 years relative, <5 years absolute)
2. Preexisting laryngeal pathology
3. Anatomic barriers
4. Coagulopathy (relative)
5. Lack of familiarity with the technique

Complications of crichothyroidotomy
1. Asphyxia
2. Aspiration
3. Creation of false passage into the tissues
4. Laceration of the trachea
5. Laceration of the esophagus
6. Hemorrhage or hematoma formation
7. Subglottic stenosis or edema
8. Laryngeal stenosis
9. Vocal cord paralysis, hoarseness
10. Mediastinal emphysema
11. Cellulitis

tor, cuffed tracheostomy tube (#6.5 and #7), two small clamps, drapes, sterile prep, and lidocaine.

Technique

Sterilely prepare and drape the neck if time permits. Identify the landmarks and immobilize the larynx between thumb and middle finger with index finger on the cricothyroid membrane. Incise the skin. The skin incision must be midline and vertical. A vertical incision leaves room for error because it can be extended in either direction to better locate the cricothyroid membrane. The incision should be made through the thyroid cartilage, membrane, and cricoid cartilage. If bleeding occurs while incising the skin, it should be ignored until after the airway has been established. Re-identify the membrane. Insert the index finger (which had been lifted slightly to allow the skin incision to be made) into the incision to re-identify the membrane. The finger should be left in the incision on the inferior aspect of the thyroid cartilage or on the superior aspect of the cricothyroid membrane to provide a guide for the incision. Incise the membrane. The membrane should be incised transversely using a #11 blade in the inferior third of the cricothyroid membrane. The incision should be 1.5 to 2 cm long in the midline. The scalpel is then withdrawn and the index finger inserted into the cricothyroid space to identify the incision and verify its correct placement.

The index finger should never be totally withdrawn until the airway is secure. It should remain on the cricothyroid membrane (superior aspect) to act as a guide. Insert the tracheal hook. The hook should be turned transversely and directed into the incision using the index finger as a guide. Once the hook is within the airway, it is rotated in a cephalad direction and withdrawn at a 45-degree angle to provide upward gentle traction on the inferior margin of the thyroid cartilage. Insert the Trousseau dilator. The dilator should be inserted into the membrane using the hook as a guide. The dilator should be opened in the vertical diameter of the membrane. Place the tube. The cuffed tracheostomy tube should be passed through the cricothyroid space between the two prongs of the dilator. Once the tube has been placed, the trocar should be removed and the inner cannula inserted. Gently tilt the dilator and remove it. Once the tube placement has been verified by auscultation, the tracheal hook can be gently removed (52).

The contraindications and complications of cricothyroidotomy are listed in Table 5.

Conclusion

The emergency physician should be thoroughly equipped to handle any airway emergency. The physician should be well versed in the indications and contraindications for different airway techniques and be ready to manage the complications that occur with those techniques. The emergency physician should also be ready to attempt different techniques if the standard techniques fail. The technique selected should be guided by the individual case and tailored to existing medical conditions.

References

1. Talucci RC, Shaikh KA, Schwab CW. Rapid sequence induction with oral endotracheal intubation in the multiple injured patient. Am Surg 1988; 54:185–187.
2. Rotondo MF, McGonigal MD, Schwab CW, et al. Urgent paralysis and intubation of trauma patients: Is It Safe? J Trauma 1993; 34:242–246.
3. Dufour DG, Larose DL, Clement SC. Rapid sequence intubation in the emergency department. J Emerg Med 1995; 13:705–710.
4. Ligier B, Buchman TG, Breslow MJ, et al. The role of anesthetic induction agents and neuromuscular blockade in the endotracheal intubation of trauma victims. Gynecol Obstet 1991; 173:477–481.
5. Norwood S, Myers MB, Butler TJ. The safety of emergency neuromuscular blockade and orotracheal intubation in the acutely injured trauma patient. J Am Coll Surg 1994; 179:646–652.
6. Roberts DJ, Clinton JE, Ruiz E. Neuromuscular blockade for critical patients in the emergency department. Ann Emerg Med 1986; 15:152–156.
7. Murphy-Macabobby M, Marshall WJ, Schneider C, et al.

Neuromuscular blockade in aeromedical airway management. Ann Emerg Med 1992; 21:664–668.

8. Petrack EM, Hollinger I. Teaching rapid sequence intubation to pediatric emergency physicians: a pilot course. Resuscitation 1994; 28:215–219.
9. Nakayama DK, Waggoner T, Venkataraman ST, et al. The use of drugs in emergency airway management in pediatric trauma. Ann Surg 1992; 216:205–211.
10. Nakayama DK, Gardner MJ, Rowe MI. Emergency endotracheal intubation in pediatric trauma. Ann Surg 1990; 211:218–223.
11. Schoenfeld PS, Baker MD. Management of cardiopulmonary and trauma resuscitation in the pediatric emergency department. Pediatrics 1993; 91:726–729.
12. Gnauck K, Lungo JB, Scalzo A, et al. Emergency intubation of the pediatric patient: Use of anesthetic agents in the emergency department. Ann Emerg Med 1994; 23: 1242–1247.
13. Sing RF, Reilly PM, Rotondo MF, et al. Out-of-hospital rapid-sequence induction for intubation of the pediatric patient. Acad Emerg Med 1996; 3:41–45.
14. Yamamoto LG, Yim GK, Britten AG. Rapid sequence anesthesia induction for emergency intubation. Pediatr Emerg Care 1990; 6:200–213.
15. Koenig KL. Rapid-sequence intubation of head trauma patients: Prevention of fasciculations with pancuronium versus mini-dose succinylcholine. Ann Emerg Med 1992; 21:929–932.
16. Walker LA. Using rapid sequence induction to facilitate tracheal intubation. Emergency Medicine Reports 1993; 14:1–15.
17. Cork C. Fentanyl preloading for rapid-sequence induction of anesthesia. Anesth Analg 1984; 63:60–64.
18. Christian CM, Waller JL, Moldenhauer CC, et al. Postoperative rigidity following fentanyl anesthesia. Anesthesiology 1983; 58:275–277.
19. Streisand JB, Bailey PL, LeMaire L, et al. Fentanyl-induced rigidity and unconsciousness in human volunteers. Anesthesiology 1993; 78:629–634.
20. Klausner JM, Caspi J, Lelcuk S, et al. Delayed muscular rigidity and respiratory depression following fentanyl anesthesia. Arch Surg 1988; 123:66–67.
21. Gilman AG, Rall TW, Nies AS, et al. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed. Pergamon Press: New York, 1990:305, 368.
22. Green SM. Ketamine sedation for pediatric procedures: Part 2, review and implications. Ann Emerg Med 1990; 19:1033–1046.
23. Silverman SM, Culling RD, Middaugh RE. Rapid-sequence orotracheal intubation: A comparison of three techniques. Anesthesiology 1990; 73:244–248.
24. Koller ME, Husby P. High-dose vecuronium may be an alternative to suxamethonium for rapid-sequence intubation. Acta Anesthesiol Scand 1993; 37:465–468.
25. Deepika K, Bihhazi GB, Mikati HM, et al. Facilitation of rapid-sequence intubation with large-dose vecuronium with or without priming. J Clin Anesth 1992; 4:106–110.
26. Marshall RJ, Muir AW, Sleigh T, Savage D. An overview of the pharmacology of rocuronium bromide in experimental animals. Eur J Anaesthesiol 1994; 11:9–15.
27. Booij LHDJ, Knape HTA. The neuromuscular blocking agent of Org 9426. Anesthesia 1994; 46:341–343.
28. Viby-Mogensen J. Dose-response relationship and time course of action of rocuronium bromide in perspective. Eur J Anaesthesiol 1994; 11:28–31.
29. Mirakhur RK. Dose response and time course of action of rocuronium bromide. Eur J Anaesthesiol 1995; 11:23–25.
30. Tryba M, Zorn A, Thole H, Zenz M. Rapid-sequence orotracheal intubation with rocuronium: A randomized double-blind comparison with suxamethonium, preliminary communication. Eur J Anaesthesiol 1994; 11:44–48.
31. Puhringer FK, Khuenl-Brady K, Koller J, Mitterschiffthaler G. Evaluation of the endotracheal intubating conditions of rocuronium (ORG 9426) and succinylcholine in outpatient surgery. Anesth Analg 1992; 75:37–40.
32. Feldman SA. Rocuronium: onset times and intubating conditions. Eur J Anaesthesiol 1994; 11:49–52.
33. Magorian T, Flannery K, Miller R. Comparison of rocuronium, succinylcholine, and vecuronium for rapid-sequence induction of anesthesia in adult patients. Anesthesiology 1993; 79:913–918.
34. Ornstein E, Matteo RS. Pharmacokinetics of rocuronium in elderly surgical patients. Eur J Anaesthesiol 1994; 11:56–62.
35. Wierda J, Mark KH, Kleef U, et al. The pharmacodynamics and pharmacokinetics of Org 9426, a new non-depolarizing blocking agent, in patients anaesthetized with nitrous oxide, halothane and fentanyl. Can J Anaesth 1991; 38:430–435.
36. De Mey JC, Debrock M, Rolly G. Evaluation of the onset and intubation conditions of rocuronium bromide. Eur J Anaesthesiol 1994; 11:37–40.
37. Benumof JL. Management of the difficult adult airway. Anesthesiology 1991; 75:1087–1110.
38. Hals G, Sayre M. The difficult airway: Access, intervention, and stabilization. Part II: Indications and contraindications for intubation and invasive management. Emergency Medicine Reports 1996; 17:35–42.
39. Morris IR. Pharmacologic aids to intubation and the rapid sequence induction. Emerg Med Clin North Am 1988; 6:753–768.
40. Rhee KJ, O'Malley RJ. Neuromuscular blockade-assisted oral intubation versus nasotracheal intubation in the pre-hospital care of injured patients. Ann Emerg Med 1994; 23:37–42.
41. Hals G, Sayre M. The difficult airway: Access, intervention, and stabilization. Part I: Step-by-step techniques for advanced clinical management. Emergency Medicine Reports 1996; 17:23–33.
42. Grande CM, Stene JK, Bernhard WN. Airway management: Considerations in the trauma patient. Crit Care Clin 1990; 6:37–59.
43. Jorden RC. Airway management. Emerg Clin North Am 1988; 6:671–685.
44. Vacanti CA, Roberts JT. Blind oral intubation: The development and efficacy of a new approach. J Clin Anesth 1992; 4:399–401.
45. Berns SD, Patel RI, Chamberlain JM. Oral intubation using a lighted stylet vs direct laryngoscopy in older children with cervical immobilization. Acad Emerg Med 1996; 3:34–40.
46. Hung OR, Pytka S, Morris I, et al. Clinical trial of a new lightwand device (Trachlight) to intubate the trachea. Anesthesiology 1995; 83:509–514.
47. Cicala RS, Kudsk KA, Butts A, et al. Initial evaluation

and management of upper airway injuries in trauma patients. J Clin Anesth 1991; 3:91–98.

48. Afilalo M, Guttman A, Stern E, et al. Fiberoptic intubation in the emergency department: A case series. J Emerg Med 1993; 11:387–391.
49. Shearer VE, Giesecke AH. Airway management for patients with penetrating neck trauma: A retrospective study. Anesth Anal 1993; 77:1135–1138.
50. Van Stralen DW, Rogers M, Perkin RM, et al. Retrograde intubation training using a mannequin. Am J Emerg Med 1995; 13:50–52.
51. Barriot P, Riou B. Retrograde technique for tracheal intubation in trauma patients. Crit Care Med 1988; 16: 712–713.
52. Walls RM. Cricothyroidotomy. Emerg Med Clin North Am 1988; 6:725–735.

Pediatric Trauma

Matthew J. Kapklein, M.D., M.P.H.,[1] and Robby Mahadeo, M.D.[2]

Abstract

Trauma is the leading cause of death in infants and children. Caring for the pediatric trauma victim requires a systematic approach which utilizes an understanding of the anatomic and pathophysiologic characteristics that make children different from adults. Child abuse frequently presents as trauma, making a high index of suspicion for mechanism and severity of injury an important component of trauma assessment. A basic approach to managing pediatric trauma with emphasis on initial stabilization is presented, followed by discussion of specific areas including head and neck trauma, chest trauma, abdominal trauma, and extremity trauma. **Key Words:** pediatric trauma, Broselow tape, resuscitation, child abuse.

INJURY IS A MAJOR CAUSE of morbidity and mortality for children in the United States. Historically, trauma has been responsible for more deaths than all other disease types combined in nearly all pediatric age groups. Physicians involved in the care of children must have a thorough understanding of how to recognize and care for the victim of childhood trauma. Physicians who work in emergency departments must be aware of the important epidemiologic, anatomic, and pathophysiologic differences between children and adults that make care of the pediatric trauma patient unique (1). Likewise, promoting active and passive strategies for prevention of childhood injury should be a priority for pediatricians and emergency medicine physicians individually and collectively.

The primary survey used in the initial evaluation and stabilization of the pediatric trauma patient proceeds along the same mnemonic, "ABCDE," as used in adult patients: Airway, Breathing, Circulation, Disability, and Exposure (2, 3). This can be expanded with the letters, "FGH": Foley, Gastric tube, and History. A secondary survey follows which involves a more in-depth physical examination. The evaluation and management approaches discussed herein should serve as general guidelines, rather than strict algorithms. Although the approach is presented here in a stepwise fashion, it is important to remember another helpful mnemonic, "AIR," which stands for Assessment, Intervention, and Reassessment after each intervention (1). Frequent measurements of vital signs—every 5 minutes during the primary survey and every 15 minutes thereafter—are recommended (2), as are serial physical examinations.

Initial Assessment: The Primary Survey

Upon first contact with the pediatric trauma patient, the immediate focus of attention is evaluation and maintenance of a patent airway. (This is discussed in detail under "Airway"). While this occurs, a brief initial history is obtained which includes the child's age and approximate weight, the time since and mechanism of injury, and the child's condition immediately after the incident. An accurate assessment of the child's weight is crucial for determining appropriate interventions, including doses of emergency medications. There is an excellent correlation in most infants and children between their length and weight. The Broselow Pediatric Resuscitation Measuring Tape is based on this correlation and provides an

---

From the Department of Emergency Medicine, Mount Sinai School of Medicine, New York. [1]Pediatric Residency Program Coordinator, Elmhurst Hospital Center, Queens, NY. [2]FAAP, Assistant Professor, Associate Director of Pediatric Emergency Medicine, Mount Sinai School of Medicine, New York. Address correspondence to Robby Mahadeo, M.D., Box 1149, Mount Sinai School of Medicine, Department of Emergency Medicine, One East 100th Street, New York, NY 10029.

easy, rapid guide for selecting appropriate equipment sizes and medication doses (3).

Various scoring systems exist for adult trauma; the best known is the Revised Trauma Score. This scale uses the Glasgow Coma Score (GCS), systolic blood pressure, and respiratory rate to assess the severity of trauma. Experience has shown this score to be less useful in children. A more reliable instrument is the Pediatric Trauma Score (PTS; see Table 1) (4).

Airway: The first step in managing the victim of trauma is a careful assessment of the airway. If a patent airway is present, it must be maintained; if a patent airway is not present, it must be obtained immediately. This can often be achieved with proper positioning alone. Pediatric airways differ from those of adults in many respects (outlined in Table 2) (1).

Children with head injuries, depressed consciousness, neck pain, paresthesias, or weakness should be presumed to have cervical spine injuries until proven otherwise. They should be placed in a cervical collar with in-line immobilization. In the trauma victim, basic airway maneuvers requiring manipulation of the cervical spine should be avoided; the chin-lift/jaw-thrust maneuver should be used to open the airway. The oropharynx must be cleared of debris and carefully suctioned. Placement of a nasopharyngeal airway in a conscious patient, or an oropharyngeal airway in an unconscious patient, may be necessary to maintain airway patency.

Indications for intubation include airway obstruction, respiratory failure, flail chest, severe hypoxia, obtundation (GCS < 8 or absence of gag reflex), need for prolonged mechanical ventilation, or inability to adequately perform bag-valve-mask ventilation. Intubation is performed using an appropriately sized endotracheal (ET) tube (Table 3). Uncuffed tubes are recommended in children younger than 8 years of age. Gastric decompression may be considered before intubation of children with gag reflexes present; otherwise, cricoid pressure (Sellick maneuver) is recommended during intubation to minimize the risk of aspiration. There are several anatomic aspects that must be considered when intubating the pediatric airway (see Table 2).

Once intubation has been accomplished, the assessment of correct ET tube placement is crucial. The short pediatric trachea makes intubation of the right mainstem bronchus common. The

TABLE 2

Special Considerations in Managing the Pediatric Airway

Opening the airway
- Infants and children have a large head-to-body ratio which results in flexion of the neck when the child is supine on a flat surface; a shoulder roll may be of use in attaining the optimal "sniffing" position of neck flexion and head extension.
- The small oral cavity and relatively large tongue often result in obstruction of the airway by the tongue; an oral airway in an unconscious child may be sufficient to move the tongue and obtain airway stability.

Intubating the airway
- Infants and children have a large amount of adenoidal tissue which makes nasotracheal intubation difficult.
- The larynx is cephalad and anterior; during intubation of infants and small children, it is often necessary to use a straight blade to gently lift the "floppy," omega-shaped pediatric epiglottis.
- The narrowest point of the airway is the cricoid ring, rather than the vocal cords; uncuffed endotracheal tubes are recommended to prevent subglottic stenosis.
- The trachea is short, making right mainstem bronchus intubation common.

Surgical airway
- The tracheal diameter is narrow and the distance between tracheal rings short. This makes emergency tracheostomy difficult and carinal perforation a potential complication.

Reprinted and modified from: Inaba AS, Seward PN: An approach to pediatric trauma: unique anatomic and pathophysiologic aspects of the pediatric patient. Emerg Med Clin North Am 1991; 9:523–548.

TABLE 1

Pediatric Trauma Score[a]

Component	+2	+1	−1
Weight	>20 kg	10–20 kg	<10 kg
Airway	Normal	Maintainable	Unmaintainable
Systolic blood pressure	>90 mg Hg or palpable at wrist	50–90 mm Hg or palpable at groin	<50 mm Hg or not palpable
Mental status	Awake	Obtunded or unconscious	Comatose or decerebrate
Skeletal injury	None	Closed fracture	Open or multiple fractures
Cutaneous injury	None	Minor	Major or penetrating

[a] A PTS greater than 8 is associated with a 0% mortality, PTS less than zero with a 100% mortality.

Reprinted from: Tepas JJ III, Ramenofsky ML, Mollitt DL, Gans BM, DiScala C. The pediatric trauma score as a predictor of injury severity: an objective assessment. J Trauma 1988; 28:425–429.

TABLE 3
Endotracheal Tube Size and Placement Calculation

Newborn[a]

Weight	Laryngoscope blade	ETT Size	ETT Depth (at Upper Lip)
1–2 kg	Miller 0	3.0	7 cm
2–3 kg	Miller 0	3.5	8 cm
3–4 kg	Miller 0–1	3.5–4.0	9 cm
>4 kg	Miller 1	4.0	10 cm

Child[b]

Age	Laryngoscope Blade	ETT Size	ETT Depth (at Gums)
1–18 mo	Miller 1	3.5–4.0 uncuffed	9–10 cm
18 mo–8 yr	Miller 2, Macintosh 2	4+ (Age/4) uncuffed	12+ (Age/2)cm
>8 yr	Macintosh 3	4+ (Age/4) cuffed	12+ (Age/2)cm

[a] Reproduced with permission. Modified from Textbook of Neonatal Resuscitation, 1987, 1990, 1994. Copyright American Heart Association.

[b] Reprinted from Seidel J. Resuscitation. In: Crain EF, Gershel JC, Gallagher EJ, editors, Clinical Manual of Emergency Pediatrics; McGraw-Hill: New York, NY: 1997, pp. 1–23.

chest wall should rise symmetrically, without abdominal movement. Auscultation over the axillae and epigastrium is recommended; however, breath sounds are easily transmitted over the entire trunk in children, making the presence of bilateral breath sounds an unreliable indicator of proper ET tube placement. Consequently, capnography is a valuable adjunct to intubation. Minute changes in ET tube position may result in significant changes in aeration, which emphasizes the need for constant reassessment during tube taping and throughout the resuscitation (7).

In circumstances in which intubation is contraindicated or unattainable, as in the case of maxillofacial injury, cricothyroidotomy may be necessary. This is best attempted as a needle cricothyroidotomy with a 14- to 18-gauge intravenous catheter placed through the cricothyroid membrane; when the needle is removed, the hub of the catheter may be attached directly to a connector from a neonatal ET tube, which in turn may be attached to a bag-valve system to provide direct oxygenation for up to 30 minutes (8). Emergency surgical tracheostomy is a difficult procedure and is best attempted by an experienced pediatric surgeon (9).

Breathing: Once the airway is secured, the respiratory status, work of breathing, and impedances to ventilation are assessed. Supplemental oxygen is recommended for all trauma victims; it may be delivered via face mask, nasal cannulae, or ET tube. Key components of the examination are assessment of vital signs (Table 4) (10) and mental status, auscultation of breath sounds, evaluation of the use of accessory muscles or presence of nasal flaring, and assessment of chest wall appearance and movement. Pediatric trauma patients, and sick children in general, are prone to aerophagia, which may significantly increase the work of breathing through compression of the diaphragm. This may be relieved quickly through placement of a nasogastric or orogastric tube.

Breathing may be compromised by pneumothorax or hemothorax; this may be the direct result of thoracic trauma, or a complication of endotracheal intubation or central venous line placement. Physical findings of a pneumothorax include asymmetric breath sounds or tympany, paradoxical breathing, tracheal deviation, subcutaneous emphysema, pulsus paradoxus, and jugular venous distension. Tension or open pneumothorax, massive hemothorax, and flail chest

TABLE 4
Pediatric Vital Signs

Age	Weight	Heart Rate	Systolic Bp	Respiratory Rate
Premature	2 kg	120–180	40–60	55–65
Newborn	3 kg	90–170	52–92	40–60
1 mo	4 kg	110–180	60–104	30–50
6 mo	7 kg	110–180	65–125	25–35
1 yr	10 kg	80–160	70–118	20–30
2 yr	12 kg	80–130	73–117	20–30
4 yr	16 kg	80–120	65–117	20–30
6 yr	20 kg	75–115	76–116	18–24
8 yr	25 kg	70–110	79–119	18–22
10 yr	30 kg	70–110	82–122	16–20
12 yr	40 kg	60–110	84–128	16–20
14 yr	50 kg	60–105	84–136	16–20

Reprinted and modified with permission from: Iliff A, Lee VA. Pulse rate, respiratory rate, and body temperature of children between two months and eighteen years of age. Child Dev. 1952; 23:237–245.

require immediate intervention. Tension pneumothorax is decompressed by placement of a large-bore intravenous catheter into the second intercostal space in the midclavicular line on the affected side, or the fourth or fifth intercostal space in the axillary line (2); the plastic catheter may be left in place until chest tube placement. It is recommended that an open pneumothorax be sealed with lubricated gauze until chest tube placement. Flail chest frequently requires intubation and positive-pressure ventilation (11). Tube thoracostomy, when necessary to relieve massive hemothorax, is performed in the fifth intercostal space in the midaxillary line (12). Replacement of blood evacuated from pleural space via autotransfusion is effective when available.

Initial ventilator settings for the intubated trauma patient include an FiO_2 of 100%, a respiratory rate approximating the normal rate for the patient's age (Table 4), and physiologic positive end-expiratory pressure (PEEP) of 3 to 5 mm Hg, which may be contraindicated in cases of head trauma or elevated intracranial pressure. For children weighing less than 10 kg, a pressure-cycled ventilator is usually preferred; the peak inspiratory pressure (PIP) is a preselected parameter and inspiration ends when that pressure is reached in the ventilator circuit. The initial PIP is set at the pressure needed for adequate chest wall movement as determined by a manometer during bag-valve ventilation, usually between 20 and 25 mm Hg for infants. For larger children, a volume-cycled ventilator is used; the initial tidal volume is set at 10–12 cc/kg, with the goal of ventilator-returned tidal volume of 7–8 cc per kilogram.

Circulation: Hypovolemic shock is not defined by the systolic blood pressure, but rather by a clinical state of diminished end-organ perfusion and oxygenation. In children, hypotension is a late and usually sudden finding. Healthy children can effectively increase their systemic vascular resistance, and hypotension from hemorrhage is rarely seen unless a child has lost more than 45% of blood volume (1, 3). One of the earliest signs of loss of intravascular volume in children is usually tachycardia. Children can tolerate increases in heart rate well and for long periods; in infants and small children, the small heart size precludes large increases in stroke volume, so cardiac output is usually directly proportional to heart rate. Other early signs of shock include delayed peripheral capillary refill (greater than 2 seconds), cool extremities, thready or diminished peripheral pulses, narrow pulse pressure, and tachypnea. Table 4 lists age-specific indices for blood pressure in children; the formula $BP = 90 + (2 \times \text{age in years})$ estimates the predicted 50th percentile for systolic blood pressure, whereas $BP = 70 + (2 \times \text{age in years})$ estimates the lower limit of normal. Diastolic blood pressure should be approximately two thirds of the systolic (7). Along with hypotension, late signs of shock include diminished consciousness, weak central pulses, cyanosis, mottling, and pallor (3).

Intravenous access is best guided by the "60-second rule." If intravenous catheters cannot be placed into peripheral veins within 1 minute of attempting, other routes are recommended. A newborn whose umbilicus has not yet detached is a candidate for an umbilical venous catheter. In infants and children up to 6 years of age an intraosseous needle is recommended. The needle is inserted into the anterior surface of the tibia of an uninjured extremity, 1–3 cm below the tibial tuberosity, perpendicular to the bone, using a screwing motion, until a sudden drop in bony resistance is achieved. Placement is ideally confirmed by return of bone marrow upon aspiration, but often the only indications of proper placement are that the needle stands upright without support and fluid flows freely without infiltration into surrounding tissue. Intraosseous needles may be used for infusion of fluids and medications, as well as aspiration for most blood tests, except the complete blood count (7). If lower extremity or pelvic fractures are suspected, or if access in the tibia is not possible, other bones suitable for intraosseous line placement are the distal femur and the distal humerus. Intraosseous access is discontinued once central or peripheral venous access is established.

Volume resuscitation in pediatric trauma victims begins with a 20 cc/kg bolus of crystalloid, either lactated Ringer's or normal saline solution. This is repeated until either the patient's hemodynamic status normalizes or the patient has received 40–60 cc/kg of solution and is still unstable, in which case packed red blood cells are rapidly administered in volumes starting with 10 cc/kg (11). Unmatched type O, Rh-negative blood may be used if transfusion is essential before patient-specific typing is available (3). Immediate surgical consultation is necessary for the unstable patient requiring rapid infusions of blood products. Visible sources of bleeding are best controlled with direct pressure and elevation. The use of the pneumatic antishock garment (PASG) in the patient unresponsive to fluid resuscitation is controversial; PASG is contraindicated in penetrating chest trauma. Use of inotropic agents should be avoided; hypotension should be assumed to be caused by inadequate preload and treated with aggressive intravascular volume resuscitation.

Serial measurements of vital signs, mental status, and pulse oximetry are necessary for continued reassessment of the patient's cardiopulmonary and hemodynamic status and should be documented every 5 to 15 minutes. Continued monitoring of urine output, usually via Foley catheter placement, is recommended to assess renal perfusion. Serial hematocrits are usually obtained, and intra-arterial monitoring may be necessary. Throughout the resuscitation, the child's large surface-area-to-mass ratio and the adverse effects of hypothermia make maintenance of normal temperature a necessity; warmed fluids, radiant warmers, overhead lamps, and thermal blankets should be used as needed.

If identified injuries are inconsistent with the degree of shock, the presence of occult injuries should be investigated. Isolated head trauma and closed extremity fractures rarely present as hypovolemic shock in a child older than 3 years of age. In addition to blood loss, other causes of shock in the pediatric trauma patient include pericardial tamponade and spinal cord injury, both of which should be considered during the initial physical examination. A suspected intracranial injury with possible elevated intracranial pressure is not a contraindication for the administration of large amounts of fluid to treat shock; in most cases, hemodynamic stabilization takes priority in the resuscitation effort.

Disability: Once ventilatory and circulatory emergencies have been addressed, the child's neurologic status must be assessed with a brief neurologic examination. Level of consciousness may be assessed rapidly using the "AVPU" scale: Alert and responsive, responsive to Verbal stimuli, responsive to Painful stimuli, or Unresponsive (3). Further, the GCS has been modified for use with preverbal children (Table 5) (13). A GCS of 14 or 15 is consistent with minor or no brain injury, whereas GCS < 8 is consistent with severe brain injury and usually requires intubation.

The assessment for disability includes an examination of pupils looking for size, reactivity, and symmetry. Eye movements are assessed for range of motion and preservation of conjugate gaze. Extremities are evaluated for tone, reflexes, and motor response. A rectal examination is performed to assess sphincter tone and, in males, the location of the prostate. Frequent re-examinations with serial determinations of the GCS are crucial for detecting subtle deteriorations in the child's status.

TABLE 5
Modified Glasgow Coma Score for Preverbal Children

Task	Performance	Score
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best verbal response	Appropriate words, coos and babbles, smiles or fixes	5
	Cries consolably, aware of environment, uncooperative	4
	Cries inconsolably/persistently, irritable, unaware	3
	Moans, agitated, restless	2
	None	1
Best motor response	Normal spontaneous movements	6
	Localizes pain, withdraws to touch	5
	Withdraws to pain	4
	Abnormal flexion/decorticate	3
	Abnormal extension/decerebrate	2
	None	1

Reprinted from: Rubenstein JS, Hageman JR. Monitoring of critically ill infants and children. Crit Care Clin 1988; 4:621–639.

Exposure: All trauma patients must be completely disrobed to allow full evaluation of injuries. The patient is examined from head to toe, including areas under bandages, the cervical collar, splints and other immobilization devices. Every patient must be carefully rolled with manual spinal stabilization to examine the back. During this part of the evaluation, both the severity of injury and the mechanisms of injury are assessed. Often the mechanism of injury is clear-cut on presentation, whereas at other times these mechanisms must be carefully investigated. It is not unusual for injury inflicted with child abuse to be attributed to some other mechanism by the child's caretaker. Any pattern of injury inconsistent with the proposed mechanism should raise the suspicion of abuse: the child with multiple facial fractures who "just fell off the bed" or the child with a bruised back who "tripped while running." Similarly, any mechanism of injury inconsistent with the child's developmental stage is suspicious; infants do not roll over at 8 weeks, toddlers do not climb at 9 months. The cause of injury in any child with apparent multiple sites and directions of blunt trauma, with injuries of varying ages, or unusually patterned lesions such as looped or hand-shaped marks or round burns, should be considered highly suspicious. A small child hit by a car while playing alone in the street at night is

TABLE 6

Areas of Focus When Examining a Child Suspected of Abuse or Neglect

- General appearance and weight-for-age: Malnutrition or chronic ill-appearance may be a sign of abuse or neglect.
- Scalp: Signs of hair-pulling or subgaleal hematoma may be present.
- Fundoscopy: Retinal hemorrhages are a cardinal sign of shaken-baby syndrome.
- Mouth: Frenulum may be torn, commissural fissuring and tears or gingival and palatal contusions may be present in forced penetration.
- Trunk: Children rarely bruise accidentally on the trunk.
- Extremities: Humeral and femoral spiral fractures are rare in the absence of inflicted injury in preambulatory children.
- Genitalia and rectum: Signs of penetration or genital contusion may be present.
- Skin: Patterned bruises, rope or wire marks on ankles, wrists and mouth may exist.

probably being neglected. Table 6 lists important areas to be considered during the examination of a child in whom abuse is suspected. A camera is an essential piece of equipment to have available during trauma resuscitation for documentation of size and nature of all injuries. Clues obtained during the physical examination can be pursued when additional history is obtained later and can help direct the physician to obtain the appropriate diagnosis. Referral to social services is essential. Physicians are required by law to report any suspicion of abuse or neglect to the child welfare authorities with jurisdiction.

Foley and Gastric Tube: Continued monitoring of renal perfusion, careful control of volume status, and serial examination of urine for gross blood is often necessary after initial resuscitation, making the placement of a Foley catheter a frequent event. Urinalysis, urine toxicology, and urine pregnancy test, when appropriate, may be obtained at this time. Relative contraindications to catheter placement include gross blood at the urethral meatus, perineal hematoma, scrotal hematoma, high-riding or boggy prostate on rectal examination, or pubic bone tenderness. A retrograde urethrogram can be performed to assess the patency of the urethra. Urologic consultation is recommended in these cases.

Decompression of the stomach is recommended via placement of an appropriately sized nasogastric tube; an orogastric tube is preferred when facial fractures or cerebral spinal fluid (CSF) rhinorrhea are present, or when a cribriform plate fracture is suspected. Large-bore tubes sometimes used for gastric decompression may potentially compromise a small child's airway, particularly if the child is already in respiratory distress.

History: A brief additional history is obtained once immediately life-threatening injuries have been addressed. An "AMPLE" history (2) includes: Allergies, Medications, Past medical and surgical illnesses, time of Last meal, and Events preceding the injury. In considering potential child abuse and neglect, historical factors associated with increased risk include chronic illness, developmental disability, multiple hospital visits for trauma, and foster care.

The secondary survey, during which each body region is thoroughly assessed in turn, serves as an opportunity for more detailed evaluation and intervention. This is also the time for appropriate diagnostic studies, including radiographic evaluation. The minimum "standard" radiographs for patients with multiple trauma include a cervical spine series, chest, and pelvis.

Head and Neck Trauma

Head injury is common and is the most frequent cause of morbidity and mortality in pediatric trauma. The physical examination is focused on signs of intracranial pathology such as bulging fontanelles, abnormal skull transillumination, or signs of basilar skull fracture which include hemotympanum, CSF rhinorrhea, or otorrhea, and the presence of Battle's sign or "raccoon eyes." A careful neurologic examination is critical. Maxillofacial trauma is assessed by palpation of bony prominences and teeth. Special emphasis is placed on the eye examination, looking for pupillary response, hyphema, papilledema, abnormalities of ocular movements, and retinal hemorrhages. The presence of retinal hemorrhages suggests the "shaken baby syndrome" and should prompt a search for other evidence of child abuse; other components of the syndrome include subdural hematomas, posterior rib fractures, and metaphyseal fractures of the long bones. Although Cushing's triad of bradycardia, hypertension, and respiratory dysregulation is a reliable sign of intracranial hypertension, neither it nor papilledema are sensitive indicators (7). The radiographic study of choice for evaluation of head injury is computerized tomography (CT); it is indicated for any trauma patient with an altered mental status or other central neurologic symptom, suspected fractures, CSF leak, or suspected intracranial hypertension.

Management of elevated intracranial pressure currently centers on maintenance of cerebral perfusion pressure (CPP). CPP is defined as the difference between mean arterial pressure (MAP) and intracranial pressure (ICP); normal ICP in a child is less than 15 mm Hg, but in an infant the upper limits of normal are 8 to 10 mm Hg (11). Principles of management include optimal oxygenation and ventilation with advanced airway management, maintenance of adequate cerebral perfusion pressure through support of systemic arterial pressure, prompt correction of hyperthermia, hypoglycemia, or hyperglycemia, and selective use of head elevation, sedation, analgesia, and hyperosmolar therapy. Management should be done in consultation with a neurosurgical service, and placement of an intraventricular catheter to monitor ICP may be necessary.

Cervical and other spinal cord injuries are less common in children than in adults but do occur, and frequently do so without radiographic evidence. This is known as SCIWORA, Spinal Cord Injury Without Radiographic Abnormality. Anatomic features of the cervical spine of children are presented in Table 7 (1). Because of the unpredictable value of cervical spine radiographs, neurosurgical consultation is recommended before removal of immobilization—even if cervical spine x-rays are normal—if any significant physical findings are present, such as numbness, paresthesias, weakness, tenderness over spinous processes, or if any historical elements suggest cervical spine injury.

Thoracic Trauma

Thoracic injury is uncommon in children, but it most frequently occurs as a result of blunt trauma. Flexible ribs and the absence of fat and muscle overlying the chest may result in significant forces being transmitted to thoracic organs from blunt trauma. Significant intrathoracic organ trauma usually occurs in the absence of rib fractures; the presence of fractures suggests massive traumatic force and is predictive of severe organ injury. In addition to the life-threatening thoracic injuries which should be identified during the initial assessment, there are several injuries of particular concern in the pediatric population.

TABLE 7

Features of the Pediatric Cervical Spine

- Incomplete ossification: Making interpretation of bony alignment difficult.
- Increased pre-odontoid space (between anterior arch of C1 and anterior aspect of odontoid process): Seen in 20% of normal children, but a distance of greater than 4–5 mm suggests atlantoaxial subluxation.
- Pseudosubluxation of C2 on C3: Seen in up to 40% of children younger than 7 years and up to 20% of children younger than 16.
- Widening of prevertebral spaces during respiration and positioning, and due to increased retropharyngeal lymph tissue. Normal prevertebral space values for children are: under 7 mm anterior to C2, under 5 mm or 40% of anteroposterior diameter of the vertebral bodies anterior to C3–4, and under 2 mm anterior to C7.

Reprinted and modified from: Inaba AS, Seward PN: An approach to pediatric trauma: unique anatomic and pathophysiologic aspects of the pediatric patient. Emerg Med Clin North Am 1991; 9:523–548.

The most common type of injury is pulmonary contusion, which may lead to respiratory failure and require aggressive ventilatory management. These patients may have few findings initially, which then progress to rales, hemoptysis, and hypoxia as signs of consolidation appear on the chest x-ray. This diagnosis must be suspected based on the mechanism of injury, and the child should be observed and reassessed for 24 hours to rule out this injury. Traumatic asphyxia, which is unusual in adults, results from sudden thoracic compression against a closed glottis. These patients may present with upper body petechiae, respiratory distress, disorientation, periorbital edema, retinal and subconjunctival hemorrhages, hemoptysis, pneumothorax, cardiac contusion, or hepatic injury. Most children with traumatic asphyxia recover with supportive care over several days (1).

Hemothorax is usually the result of injury to the intercostal vessels. Fracture of the first rib in conjunction with an apical hematoma or hemothorax is suspicious for an aortic injury or cardiac contusion; cardiac contusion often has a normal electrocardiogram. Classic findings of aortic disruption are chest and midscapular pain accompanied by lower body hypoperfusion and upper body hypertension; unfortunately classic findings are not usually evident. Multiple posterior rib fractures are suspicious for shaken baby syndrome.

Abdominal and Pelvic Trauma

Blunt abdominal trauma accounts for the vast majority of abdominal injuries in children. The spleen and liver are the most commonly injured organs. Absence of overlying fat and muscle in children make their abdominal organs more susceptible to injury than in adults, and often these injuries occur with minimal or no external evidence (3). Physical examination, best performed after bladder and gastric decompression, may give important clues to diagnosis. The presence of ecchymoses, abrasions, distension, rigidity, tenderness, or masses are all indicators of traumatic pathology. However, children who are agitated or have depressed consciousness are difficult to examine for tenderness, and the clinician may have to rely on diagnostic studies. Surgical consultation with a pediatric surgeon should be obtained in all cases of abdominal trauma. In addition to a complete blood count, recommended laboratory studies include urinalysis for hematuria, serum amylase and lipase (trauma is one of the most common causes of pancreatitis in children), and serum transaminases.

Abdominal CT is the preferred investigational tool in children to assess for intra-abdominal injury. Indications to consider obtaining a CT include a tender abdomen on examination, or an unreliable examination with a suspicious mechanism of injury. Laparotomy is considered when the child has ongoing fluid or blood requirements without an obvious bleeding source. Plain radiographs of the chest or abdomen are neither sensitive nor specific, although they may occasionally yield clues to intra-abdominal pathology such as an elevated hemidiaphragm, displaced gastric bubble or abdominal gas, or pleural effusion. Isolated splenic and hepatic injuries in children are frequently managed conservatively, and most children with isolated spleen injuries do not require transfusions or surgery. If splenectomy is considered, however, the patient should receive pneumococcal and meningococcal vaccines preoperatively.

The role of diagnostic peritoneal lavage (DPL) in evaluating trauma in pediatric patients is limited because the presence of blood in the peritoneum does not necessarily indicate the need for exploratory laparotomy. DPL is invasive and painful, does not identify the specific organ injured, and does not necessarily identify *retro*peritoneal injury (1).

Traumatic pelvic injury is common in children, but is usually confined to the soft perineal tissues from straddle injury. Pelvic fractures are uncommon. Nonetheless, physical findings suspicious of pelvic fracture, such as bony tenderness or instability, or any of the signs of urethral injury previously discussed, should prompt evaluation with pelvic radiographs.

Every pediatric trauma victim should receive a thorough genital evaluation. Findings consistent with sexual abuse such as lacerations, abrasions, and contusions of the perineum should be carefully noted. Other suspicious findings include marked enlargement of the hymenal ring in girls (normally about 1 mm in diameter per year of age) with thickening and notching, lichenification, genital warts, or evidence of other sexually transmitted disease. In prepubertal girls with external evidence of traumatic sexual abuse, the likelihood of internal injury is great, and examination under anesthesia is indicated.

Extremity Trauma

Closed extremity injuries are rarely life-threatening, and are usually addressed in the secondary survey. With the exception of children younger than 3 years of age, closed femur fracture alone cannot be considered sufficient cause for hemodynamic instability and other sites of bleeding should be sought. In addition to open hemorrhage and neurovascular injury, it is important to assess for the presence of compartment syndrome. This occurs when muscular ischemia results from hemorrhage or edema in the relatively inelastic fascial compartment of an extremity. Pain on active or passive stretching is usually the first sign. Injuries that generally produce the syndrome are supracondylar distal humeral fracture, elbow dislocations, proximal radial and ulnar fractures, proximal tibial and distal femoral fractures, displaced tarsal bone fractures, and crush injuries. The definitive treatment is emergent fasciotomy.

Fractures that are unique to children involve the growth plate and are described using the Salter-Harris classification system. Presence of the growth plates often makes radiographic assessment of the long bones in growing children difficult, and for this reason bilateral radiographs of any structure suspected of fracture are usually obtained for all prepubertal children. Other kinds of fractures seen in children include greenstick and buckle fractures (3). The shaken baby syndrome, as already discussed, is one of only two syndromes pathognomonic for abuse; the other is the presence of multiple fractures of varying ages. Once two fractures of different ages are seen in a trauma evaluation, a complete radiographic skeletal survey should be performed.

Issues in Pediatric Trauma Care

Once the secondary survey is complete, the remaining aspects of caring for the trauma patient need to be addressed. Often forgotten in the pediatric patient is the strong need for sedation and analgesia. Concern about “masking” physical findings with analgesics is often inappropriate and the evaluation and management of the patient may be greatly facilitated by the judicious use of pharmacologic agents. Certainly once the initial evaluation is complete and the principal diagnoses identified, or the decision is made for a patient to undergo an interventional or operative procedure, there is no need to delay appropriate pain management. Children require cardiorespiratory monitoring after the administration of sedatives and narcotics, and vascular access should be maintained during wound suturing, fracture reduction, or other procedures that require conscious sedation. The need for antimicrobial and tetanus prophylaxis must always be investigated. Finally, the psychosocial aspects of the case must be addressed, including careful discussion with families and patients, involvement of emergency department-based social services, and child protection services, if necessary.

Despite advances in trauma resuscitation, the best cure for pediatric trauma remains prevention. Pediatricians and emergency physicians must advocate active and passive prevention strategies, which should include age-appropriate safety advice in the care of all patients, especially those who experience minor trauma. The use of infant car seats and seat belts, "child-proofing" of homes and play environments, and use of protective sports gear such as bicycle helmets, are all issues easily addressed in the emergency department or ambulatory care setting. No discussion of trauma in the United States is complete without mention of firearms and illicit substance use. The firearm-related death rate is higher in the United States than in any other industrialized country, and much of the penetrating trauma in both pediatrics and adults is drug-related. All health care providers should work toward removing these threats from society and ensuring the safety and future for our children.

References

1. Inaba AS, Seward PN. An approach to pediatric trauma: unique anatomic and pathophysiologic aspects of the pediatric patient. Emerg Med Clin North Am 1991; 9: 523–548.
2. Haller A, Johnston C, Luten R, Singer J. Trauma. In: Silverman B, ed. APLS: The Pediatric Emergency Medicine Course, 2nd ed. American Academy of Pediatrics, American College of Emergency Physicians: Elk Grove, IL, Dallas, TX, 1993: 59–75.
3. American College of Surgeons Committee on Trauma. Pediatric Trauma. In: Advanced Trauma Life Support Course Student Manual, 4th ed. Chicago, IL: American College of Surgeons, 1992: 261–281.
4. Tepas JJ III, Ramenofsky ML, Mollitt DL, et al. The pediatric trauma score as a predictor of injury severity: an objective assessment. J Trauma 1988; 28:425–429.
5. Chameides L, ed. Textbook of Neonatal Resuscitation. Elk Grove Village, IL: American Heart Association, 1994.
6. Seidel J, ed. Resuscitation. In: Crain EF, Gershel JC, Gallagher EJ, eds. Clinical Manual of Emergency Pediatrics, 3rd ed. McGraw-Hill: New York, NY, 1997; 1–23.
7. Chameides L, ed. Textbook of Pediatric Advanced Life Support. American Heart Association: Elk Grove Village, IL, 1988.
8. Harris BH. Management of multiple trauma. Pediatr Clin North Am 1985; 32:175–181.
9. Graneto JW, Soglin DF. Transport and stabilization of the pediatric trauma patient. Pediatr Clin North Am 1993; 40:365–380.
10. Iliff A, Lee VA. Pulse rate, respiratory rate, and body temperature of children between two months and eighteen years of age. Child Dev 1952; 23:237–245.
11. Moront ML, Williams JA, Eichelberger MR, Wilkinson JD. The injured child: an approach to care. Pediatr Clin North Am 1994; 41:1201–1226.
12. King DR. Trauma in infancy and childhood: initial evaluation and management. Pediatr Clin North Am 1985; 32:1299–1310.
13. Rubenstein JS, Hageman JR. Monitoring of critically ill infants and children. Crit Care Clin 1988; 4:621–639.

The Evaluation of Blunt Abdominal Trauma:

The Evolving Role of Ultrasound

Sheree Givre, M.D.[1] and Stuart Kessler, M.D.[2]

Abstract

There is a growing body of literature pertaining to the use of ultrasound in the evaluation of patients with blunt abdominal trauma. Multiple studies have looked at the use of this modality as a screening examination for the detection of intra-abdominal fluid and as a means of diagnosing specific organ injuries. Although ultrasound has been used extensively in Europe and Asia, it has only recently been used in the United States. In many centers, ultrasound is now being performed by emergency medicine physicians and trauma surgeons as part of the initial trauma evaluation. This paper summarizes the recent literature on the use of ultrasound in evaluating blunt abdominal trauma as an adjunct or an alternative to diagnostic peritoneal lavage and abdominal computed tomography. **Key Words:** ultrasound, abdominal trauma, diagnostic peritoneal lavage, abdominal computed tomography.

ABDOMINAL TRAUMA ACCOUNTS for 10% of all trauma-related deaths. The goal of the initial evaluation of the patient who has sustained blunt abdominal injury is to rapidly differentiate those who will require immediate operative care from those who can be managed conservatively. History and physical examination may be of limited value, especially in patients with head or spinal trauma, intoxication, or distracting injuries. Even when the history and physical examination are readily obtained, they detect only 65% of significant abdominal injuries which require surgical exploration (1). For this reason, diagnostic peritoneal lavage (DPL) and abdominal computed tomography (CT) have traditionally been used in the evaluation of abdominal trauma to delineate the nature and severity of the injury. Although each of these modalities provides useful information, both have limitations. Recent studies have investigated the use of ultrasonography in the evaluation of blunt abdominal trauma, and this technique is now being used routinely in many centers.

Diagnostic Peritoneal Lavage

Diagnostic peritoneal lavage was developed by Root and colleagues in 1965 (2). In this procedure, a catheter is placed in the abdominal cavity and 1 L of fluid is lavaged in adults, 10 to 20 cc/kg in children. The standard criteria for a positive DPL are listed in Table 1. Most studies have shown that DPL is both highly specific and sensitive for the detection of intra-abdominal injuries (Table 2). The procedure can be done in the emergency department or the operating room on patients whose conditions are unstable while resuscitation measures are on-going. It can be done relatively quickly, averaging 21 minutes, or 12 minutes in cases which yield a grossly positive aspirate (3). DPL is contraindicated in patients who are pregnant, patients with prior multiple

---

From the Department of Emergency Medicine, Mount Sinai School of Medicine. [1]FACEP, Assistant Director, Department of Emergency Medicine, Elmhurst Hospital Center, Elmhurst, New York. [2]FACEP, Vice-Chair, Department of Emergency Medicine, Mount Sinai School of Medicine; Director, Department of Emergency Medicine, Elmhurst Hospital Center, Elmhurst, New York. Address correspondence to Sheree Givre, M.D., Elmhurst Hospital Center, Department of Emergency Medicine, 79-01 Broadway, Elmhurst, NY 11373.

TABLE 1
Criteria for a Positive DPL

Aspiration of >5 mL of gross blood
RBC count of >100,000/mm
WBC count of >5,000/mm
Amylase level of 200 IU/100 mL
Bile or bacteria present
Return of lavage fluid into chest tube or Foley catheter

DPL, diagnostic peritoneal lavage; RBC, red blood cell; WBC, white blood cell.

TABLE 2
Comparison of DPL, CT, and US

			US (3)	
	DPL (1)	CT (1)[b]	Intraperitoneal Fluid	Organ Injury
Sensitivity	98	60–88	87–100	69–96
Specificity	92	98	99–100	95–100
Accuracy	80	92	90.9–97	
PPV	82	88	Varies	
NPV	100	84–97	Varies	

[a] Values stated are percents. DPL, diagnostic peritoneal lavage; CT, computed tomography; US, ultrasonography; PPV, positive predictive value; NPV, negative predictive value.
[b] Higher values represent more recent studies.

abdominal incisions, or patients who have a fractured pelvis. Limitations of the procedure include the inability to evaluate the retroperitoneum, to make organ-specific diagnoses, or to assess the severity of injury. DPL can not detect contained subcapsular or intraparenchymal hematomas, and will miss diaphragmatic or bowel wall injuries. False positive results occur in only 1.4% of cases and are usually due to trauma from catheter insertion, retroperitoneal hematoma, or minor lacerations of the liver and spleen (4). DPL is a safe and easy procedure to perform with a complication rate of only 1%; the major complications include laceration of iliac or mesenteric vessels and perforation of intestines or bladder. DPL can alter the results of subsequent physical and diagnostic examinations.

Abdominal Computed Tomography

Computed tomography (CT) was introduced into clinical medicine in 1972 and was first used in the evaluation of blunt abdominal trauma in the early 1980s (5). Level I and II trauma centers must be equipped with CT facilities that are available 24 hours a day. CT is both a sensitive and specific modality for the detection of intra-abdominal injury. (See Table 2.) It is noninvasive and can detect retroperitoneal injuries as well as identify specific organ injuries. CT can identify those hepatic and splenic injuries which can be managed conservatively. In addition, images of the spine and pelvis can be obtained simultaneously during abdominal imaging.

Use of CT in evaluating patients with abdominal trauma has several limitations. Obtaining the CT scan is a time-consuming process. CT cannot be performed on patients who are hemodynamically unstable, especially when the CT is not in close proximity to the emergency department. Complications can arise as a result of moving the patient on to or off of the CT scanner. In addition, it is not possible to perform other procedures simultaneously or to continually reassess the patient during scanning. The quality of information obtained declines when oral or intravenous contrast cannot be tolerated, and interpretation of subtle findings on CT depends on the level of training of the physician reading the scan. The reported complication rate of using CT in blunt abdominal trauma is reported to be as high as 3.4% because of aspiration of contrast, hemodynamic deterioration, and delay in determining the need for laparotomy (6).

Abdominal Ultrasound

Abdominal ultrasound has been used routinely by trauma surgeons in Europe and Asia for the past 20 years. In Germany, the teaching of ultrasonography is part of surgical residency training, and only candidates experienced in diagnostic ultrasound technique are eligible to sit for national board examinations (7). The first reported use of abdominal ultrasound in the management of blunt abdominal trauma in the United States was by Ammann in 1983 (8). Since that time, ultrasonography has been incorporated into the evaluation of blunt abdominal trauma in many centers throughout this country. Many emergency medicine (EM) residencies have begun training in ultrasonography for their residents (9).

Ultrasound is a noninvasive test that can be used in the evaluation of both blunt and penetrating trauma. The abdomen can be evaluated for the presence of intraperitoneal fluid, retroperitoneal fluid, and specific injuries to the liver, spleen, and kidneys. The thoracic cavity can be evaluated for pleural fluid and pericardial fluid. Ultrasound can be performed at the bedside of hemodynamically unstable patients, and there are no contraindications, such as past abdominal surgeries or pregnancy, to performing the test.

Figure 1 denotes the areas used in the evalu-

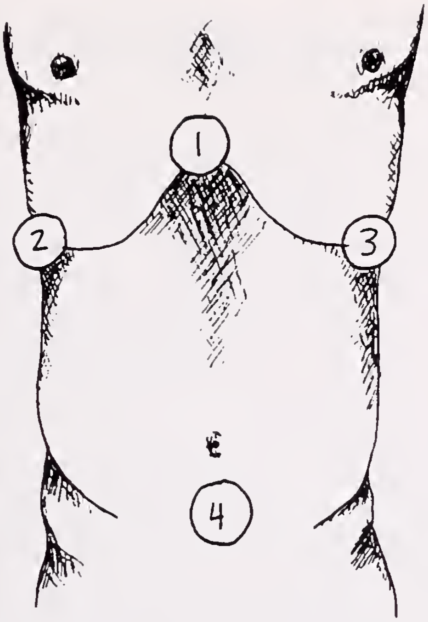


FIG. 1. Areas examined by ultrasonography in the trauma patient. See text for discussion.

ation of trauma patients. Area 1 is the subxyphoid view of the heart. It is used to look for pericardial fluid and can be used to evaluate global wall motion. Area 2 is used to examine Morrison's pouch. Intraperitoneal fluid can be seen here between the liver and right kidney, and when present, is a quick way of diagnosing intra-abdominal fluid. By moving the probe slightly and tilting it in different directions the right lower thoracic cavity, the liver, the right kidney, and the right retroperitoneum and paracolic gutter can be visualized. Area 3 is used to visualize the spleen, free perisplenic fluid, the left retroperitoneum, and the left paracolic gutter. Area 4 gives a view of the bladder, uterus, or prostate, and the lateral walls of the pelvis; it is used to visualize fluid in the pouch of Douglas.

With improvements in technology, portable and relatively inexpensive ultrasound machines with good resolution are now available. Many emergency departments are equipped with these machines to evaluate patients for ectopic pregnancy and cholelithiasis. In departments already possessing this technology, there are no additional capital costs incurred by using it in the evaluation of the patient with blunt abdominal trauma. There are limitations to the use of sonography in blunt abdominal trauma. Ultrasonographic studies depend on the expertise of the ultrasonographer, although there is a steep learning curve. Examinations may be difficult to interpret in obese patients and patients with subcutaneous emphysema, with an ileus, and with prior abdominal surgery. As with all examinations done on patients with blunt abdominal trauma, it may be difficult to perform on an uncooperative patient.

Ultrasound can be done rapidly on hemodynamically unstable patients while resuscitation is in progress. Healy (10) did a prospective study of the use of ultrasound in blunt abdominal trauma which included an analysis of the time required to perform the examination. The examination was completed in 2 to 24 minutes, with mean time for completion of 10.1 minutes. The studies were performed by an ultrasound technician and were observed in real time by an attending trauma surgeon and a radiology resident. Management decisions were based on the surgeon's interpretation of the sonogram. Although other studies have not analyzed the time required to perform the ultrasound, several studies have stated that less than 5 minutes is required to detect free fluid. This is significantly less than the time required to perform DPL (11–18). In addition, because of its low cost, rapidity, and portability, serial ultrasound examinations can be done to evaluate fluid accumulation. If a small amount of fluid is visualized on the initial examination, repeat sonograms can be easily obtained to monitor potential progression.

It has been suggested that a small quantity of intraperitoneal fluid may be missed when ultrasounds are performed by nonradiologists. The quantification of intra-abdominal fluid has been investigated in several studies (15, 18, 19). Branney et al. (19) found that less than 10% of ultrasonographers were able to detect a fluid volume of 400 mL or less in Morrison's pouch. Goletti et al. (15) used a cut-off of 250 mL of free fluid in stable patients to determine the need for surgery. In their experience amounts of 250 mL or less of free fluid correlated with a high rate of unnecessary laparotomy. The major difference between the two studies is the experience of the ultrasonographers. In Branney's study, quantification of fluid was done by residents and attending physicians in emergency medicine, surgery, and radiology. Except for the radiology attendings, all others had minimal training and experience in ultrasonography. In Goletti's study, sonograms were performed by trauma surgeons with at least 2 years experience. It can be concluded that the ability to detect small amounts of fluid is a function of training and experience. However, large amounts of fluid can be easily detected with minimal training in ultrasonography and can expedite the decision-making process in prioritizing trauma management; small amounts of fluid are usually seen on patients who can be managed conservatively. As emergency medicine physicians and trauma surgeons become more experienced in the use of ultrasound to evaluate patients with blunt abdominal trauma, their ability to visualize small amounts of intraperitoneal fluid can be expected to increase.

Ma and colleagues (16) conducted a prospective study to determine the sensitivity, specificity, and accuracy of the rapid trauma ultrasound evaluation, performed by emergency physicians. In this study EM residents, fellows, and attending physicians were trained to perform a rapid ultrasound examination, focusing on the identification of free fluid in the pericardial sac, the pleural cavity, the peritoneal cavity, and the retroperitoneum. The training consisted of 10 hours of didactic sessions, videotape case reviews, and demonstrations of rapid trauma ultrasound examinations. Each EM physician performed a minimum of 15 to 20 ultrasound examinations on normal or nontraumatized patients before entering the study. There were 245 nonconsecutive trauma patient ultrasounds analyzed. Results of the ultrasonography were compared with CT, DPL, chest x-ray, formal two-dimensional echocardiography, and outcome findings. The rapid ultrasound examination was 90% sensitive, 99% specific, and 99% accurate. The videotaped ultrasound examinations were also reviewed by a surgical sonographer from Kobe, Japan. There was disagreement with one false-negative examination and the two false-positive examinations. The authors concluded that emergency physicians can accurately perform and interpret rapid trauma ultrasound examinations.

In a study done in Germany the influence of the investigator's experience in ultrasonography in blunt abdominal trauma was evaluated (19). Surgeons with training of less than 1 year, 1–3 years, and more than 3 years were compared. The sensitivity for intra-abdominal pathology was 100%, 100%, and 92%, and the specificity 94%, 89%, and 98% for the three levels of experience, respectively. They concluded that ultrasonography is a suitable screening test because it was highly sensitive, highly specific, free of complications, and easy to learn. However, the authors emphasized that, when learning to use ultrasound, positive findings should be verified by other methods, including ultrasound done by a more experienced sonographer. Several other studies have investigated the competency of nonradiologists in the use of ultrasound in blunt abdominal trauma (11–13, 19). All of these studies demonstrated a high sensitivity and specificity for the detection of intra-abdominal injury and suggested that ultrasound can be used by nonradiologists to rapidly evaluate patients with blunt abdominal trauma (Table 2).

Role of Ultrasound in Blunt Abdominal Trauma

The role of ultrasound in blunt abdominal trauma is rapidly evolving. However, it is still uncertain whether ultrasound should be used solely to evaluate for the presence of intra-abdominal fluid, if it should be used to look for specific organ injuries, or if it can replace DPL or CT. In a study by Liu et al. (21), the diagnostic utility of DPL, CT, and ultrasonography in blunt abdominal trauma was compared. The only difference between the three tests was the failure of ultrasound to detect isolated small bowel perforations and retroperitoneal hematomas. In other studies, ultrasound was combined with DPL to improve the diagnostic yield (15). Goletti et al. (15) incorporated the use of ultrasound-guided paracentesis in stable patients with less than 250 mL free fluid collection. The fluid was evaluated for blood, white blood cells, amylase, bilirubin, and vegetable fibers. Using this method they were able to detect lesions of the biliary tree and hollow visceral lesions.

All algorithms that use ultrasonography in blunt abdominal trauma begin with the hemodynamic stability of the patient (5, 12, 13, 15, 19, 20). Patients who are hemodynamically unstable and have an ultrasound that is positive for free fluid are candidates for immediate exploratory laparotomy. When the patient is hemodynamically unstable, and abdominal ultrasound is negative for fluid, other causes of hemodynamic compromise should be sought; serial ultrasound examinations or DPL may be used to further evaluate the abdomen.

In hemodynamically stable patients with a positive ultrasound, several management strategies are possible. The patient may go directly to exploratory laparotomy, may have an abdominal CT, or may be monitored with serial clinical or ultrasound examinations. In hemodynamically stable patients with a negative ultrasound, management may consist of serial ultrasound examinations, CT, or observation. The algorithm followed at any institution must include an assessment of the hemodynamic stability of the patient, the type of intra-abdominal injury, other injuries sustained by the patient, and the expertise of the ultrasonographer.

Pearl and Todd (22) reviewed 11 prospective trials on the use of ultrasonography in the initial evaluation of blunt abdominal trauma. They concluded that there were frequent methodologic flaws in the studies and that none of the trials determined therapeutic effect or assessed patient outcome. Although reports in the literature state sensitivity and specificity as high as 98% and 100%, respectively (23), for intraperitoneal fluid and 96% and 95% (20), respectively, for organ injuries, Pearl and Todd concluded that a well-designed controlled trial is still needed to clearly define the role of ultrasound in evaluating patients with blunt abdominal trauma.

Conclusion

Although some authors have suggested that ultrasonography will replace DPL and CT in certain clinical settings, the best approach at the present time may be to use these tests in a complementary fashion. When ultrasound is first introduced to a trauma center, it should be followed by DPL or CT to confirm all findings, unless the patient is hemodynamically unstable, in which case emergent laparotomy is indicated. As the expertise of the physicians performing the ultrasound examination improves, fewer confirmatory studies will be necessary. DPL can be reserved for unstable patients with negative ultrasound or with minimal fluid. In the latter case, ultrasound-guided paracentesis may also be done. In situations in which CT is needed to evaluate other injuries, and the patient is hemodynamically stable, ultrasonography may be unnecessary or may help to prioritize access to the CT. On the other hand, in the hemodynamically unstable patient, ultrasonography may obviate the need for CT and direct the patient to laparotomy.

Acknowledgment

Thanks to Moria McCarthy M.D. for the illustration and Syndee Givre, M.D., and Donald Barton, M.D. for their editorial assistance.

References

1. Olsen W, Hildreth D. Abdominal paracentesis and peritoneal lavage. J Trauma 1971; 11:824–828.
2. Root HD, Hauser CW, McKinley CR. Diagnostic peritoneal lavage. Surgery 1965; 57:633–638.
3. Catre M. Diagnostic peritoneal lavage versus abdominal computed tomography in blunt abdominal trauma: A review of prospective studies. Can J Surg 1995; 38:117–122.
4. Gomez G, Alverez R, Plasencia G, et al. Diagnostic peritoneal lavage in the management of blunt abdominal trauma: A reassessment. J Trauma 1987; 27:1–6.
5. Davis J, Hoyt D, MacKensie R, et al. Complications in evaluating abdominal trauma: Diagnostic peritoneal lavage versus computerized axial tomography. J Trauma 1990; 30:1506–1510.
6. McKenney M, Martin L, Lentz K, et al. 1,000 consecutive ultrasounds for blunt abdominal trauma. J Trauma 1996; 40:607–612.
7. Rozycki G. Abdominal ultrasonography in trauma. Surg Clin North Am 1995; 75:175–191.
8. Ammann A, Brewer W, Maull K, et al. Traumatic rupture of the diaphragm: Real-time sonographic diagnosis. Am J Roentgenol 1988; 140:915–919.
9. Mateer J, Plummer D, Heller M, et al. Model curriculum for physician training in emergency ultrasonography. Ann Emerg Med 1994; 23:95–102.
10. Healy MA. A prospective evaluation of abdominal ultrasound in blunt trauma: Is it useful? J Trauma 1996; 40:875–883.
11. Jehle D, Guarino J, Karamanoukian H. Emergency department ultrasound in the evaluation of blunt abdominal trauma. Am J Emerg Med 1993; 11:342–345.
12. Kimura A, Otsuka T. Emergency Center ultrasonography in the evaluation of hemoperitoneum: A prospective study. J Trauma 1991; 31:20–23.
13. Boulanger B, McLellan B, Brenneman F, et al. Emergent abdominal sonography as a screening test in a new diagnostic algorithm for blunt trauma. J Trauma 1996; 40:867–374.
14. Boulanger B, Brenneman F, McLellum B, et al. A prospective study of emergent abdominal sonography after blunt trauma. J Trauma 1995; 39:325–329.
15. Goletti O, Ghiselli G, Pippolis P, et al. The role of ultrasonography in blunt abdominal trauma: results in 250 consecutive cases. J Trauma 1994; 36:178–181.
16. Ma J, Matter J, Ogata M, et al. Prospective analysis of a rapid trauma ultrasound examination performed by emergency physicians. J Trauma 1995; 38:790–885.
17. Lucciarini P, Ofner D, Weber F, et al. Ultrasonography in the initial evaluation and follow-up of blunt abdominal injury. Surgery 1993; 114:506–512.
18. Mckenny M, Lentz K, Nunez D, et al. Can ultrasound replace diagnostic peritoneal lavage in the assessment of blunt trauma? J Trauma 1994; 37:439–441.
19. Branney S, Wolfe R, Moore E, et al. Quantitative sensitivity of ultrasound in detecting free intraperitoneal fluid. J Trauma 1995; 39:375–380.
20. Forster R, Pillasch J, Zielke A, et al. Ultrasonography in blunt abdominal trauma: Influence of the investigator's experience. J Trauma 1992; 34:264–269.
21. Liu M, Lee CH, P'eng FK. Prospective comparison of diagnostic peritoneal lavage, computed tomographic scanning, and ultrasonography for the diagnosis of blunt abdominal trauma. J Trauma 1993; 35:267–270.
22. Pearl WS, Todd KH. Ultrasonography for the initial evaluation of blunt abdominal trauma: A review of prospective trials. Ann Emerg Med 1996; 27:353–361.
23. Rothlin MA, Naf R, Amgwerd, et al. Ultrasound in blunt abdominal and thoracic trauma. J Trauma 1993; 34: 488–495.

Vascular Emergencies

DENISE C. SEMASHKO, M.D.

Abstract

This article reviews the initial assessment and emergent management of several common as well as uncommon vascular emergencies. Aortic dissection, aneurysms, and arterial occlusive disease are familiar but challenging clinical entities. Less frequently encountered conditions are also discussed including an aortic enteric fistula, mesenteric venous thrombosis, phlegmasia alba dolens, and subclavian vein thrombosis. **Key Words:** vascular emergencies, aortic dissection, aneurysm, arterial occlusion.

THE EMERGENCY PHYSICIAN is usually the first person to render care to the seriously ill patient. When the disease is readily recognized, there is little challenge to making the diagnosis. But, when the complaints are vague, a diagnostic plan must be instituted to identify conditions requiring expeditious treatment. Vascular emergencies often have critical consequences and so must be considered early in the differential diagnosis of suggestive complaints. Clinical suspicion of these conditions should begin at triage.

The initial assessment and emergent management of several common vascular emergencies such as aortic dissection, aneurysms, and arterial occlusive disease are reviewed. These are familiar but challenging clinical entities. Less frequently encountered conditions are also discussed including an aortic enteric fistula, mesenteric venous thrombosis, phlegmasia alba dolens, and subclavian vein thrombosis.

Aortic Dissection

The classic presentation of aortic dissection is an older, hypertensive man who experiences a sudden onset of severe chest pain radiating to the back and then migrating caudally. The pain is typically abrupt and of maximum intensity from its onset. Frequently, the pain is described as a ripping or tearing sensation. Involvement of the proximal aorta may give only anterior chest pain; involvement of the descending aorta often manifests itself as intrascapular pain. As a dissection progresses, the flow of blood can be interrupted anywhere along the route of the dissection, causing many associated symptoms. Occlusion of the branches of the aorta can lead to myocardial infarction, stroke or transient ischemic attack, bowel ischemia, acute renal failure, limb ischemia, and rarely, spinal cord infarct with paralysis. Proximal disruption involving the aortic valve can cause sudden cardiac failure or blood can dissect into the pericardial space causing tamponade. Syncope and gastrointestinal bleeding have also been described.

Aortic dissection is two to three times more common than abdominal aortic aneurysmal rupture. Its occurrence is more frequent between 50 and 70 years of age. Hypertension, the most consistent risk factor, occurs approximately 75% of the time (1). Other risk factors include Marfan's syndrome, Ehler-Danlos, congenital heart disease, pregnancy (usually third trimester), coarctation, Turner's syndrome, and trauma.

Aortic dissection begins with a transverse tear through the intima and into the media where a column of blood then dissects this plane either antegrade or retrograde causing the migrating pain. The site of the intimal tear is found in the ascending aorta, transverse aorta, and descend-

---

From the Department of Emergency Medicine, Mount Sinai School of Medicine, Assistant Professor of Emergency Medicine. Address reprint requests to Denise C. Semashko, M.D., Mount Sinai School of Medicine, Department of Emergency Medicine, Box 1149, One East 100th Street, New York, NY 10029.

TABLE 1
Classification of Aortic Dissection

DeBakey Type	Stanford Type	Involvement	Treatment
1	A	Ascending Transverse Descending	Surgery
2	A	Ascending	Surgery
3	B	Descending	Medical[a]

[a] Unless complicated by hemorrhage, limb or organ ischemia, intractable pain, or progression or symptoms.

ing aorta, respectively, in 70%, 10%, and 20% of cases (1). The anatomic classification is important because therapeutic intervention is based on location of the dissection. (See Table 1.) DeBakey Type 3 dissections (also called Stanford Type B dissections), begin distally to the left subclavian artery and can be managed without surgical intervention, unless they are complicated by hemorrhage, limb or organ ischemia, intractable pain, or progression of symptoms. Physical examination may reveal the murmur of aortic regurgitation if the aortic valve is involved, asymmetric upper extremity pulses, or pulse deficits in the lower extremities.

Laboratory tests are not helpful in establishing the diagnosis, but an electrocardiogram (ECG) may be helpful in ascertaining the presence of myocardial ischemia (2). The chest x-ray reveals mediastinal widening in at least 75% of cases. Other x-ray findings associated with aortic dissection include a pleural effusion, usually on the left, and what appears to be a double-channeled aorta (3).

Computed tomographic (CT) scanning is a reliable test for making the diagnosis of aortic dissection; it shows the extent of the dissection and involvement of branches of the aorta (4). More recently, transesophageal echocardiography has become a useful tool and should be used if available (5). This procedure can confirm the diagnosis by visualizing the intimal flap as well as providing information regarding myocardial function and the status of the aortic valve (6). Magnetic resonance imaging can provide detailed information about the extent and size of the dissection. Unfortunately, imaging acquisition is a lengthy process, and unstable patients are not candidates for this test (7).

Patients with an aortic dissection should receive careful monitoring of their cardiac rhythm, blood pressure, and urine output. Patients are often hypertensive upon presentation; systolic pressure should be lowered to approximately 100 mm Hg with intravenous antihypertensive therapy. The therapy of choice is sodium nitroprusside and a beta blocker. If this therapy cannot be tolerated, trimethaphan camsylate, a ganglionic blocking agent, can be instituted but rapid tachyphylaxis can develop. Calcium channel blockers have been recommended by some authors for refractory hypertension; angiotensin-converting enzyme inhibitors are effective in renal artery occlusion. Hypotension with an aortic dissection usually indicates external rupture and should be treated with aggressive blood pressure support and early surgical consultation and intervention. Pain control is important and should be addressed with appropriate therapy. If the ascending aorta (DeBakey Type 1 or 2) is involved, surgical intervention is indicated because this dissection can involve the aortic valve and the coronary arteries. Type 3 dissections involve only the descending aorta; these are usually treated medically because the nonoperative mortality is about 15% which is lower than the surgical mortality at most centers (1). Surgical intervention for descending dissections is indicated if there is occlusion of a major blood vessel, leakage, rupture, or uncontrolled hypertension. Patients with Marfan's Syndrome should have surgical intervention because of the high risk of rupture, redissection, or aneurysmal formation.

Aortic dissection is a true vascular emergency which should not be diagnosed post mortem by the pathologist. Although making the diagnosis in the Emergency Department in the face of an atypical presentation may be difficult, it is essential to do so to assure expeditious and appropriate surgical and medical therapy to limit morbidity and mortality.

Aneurysms

A true aneurysm occurs when all layers of the arterial wall, intima, media, and adventitia are involved and the overall diameter expands by at least one and one-half times. Many factors have been implicated in producing aneurysms including atherosclerosis, cigarette smoking, change in cholesterol intake, collagen disorders, and trauma. In the absence of intervention, aneurysms tend to increase in size and, depending on location, they may rupture, thrombose, or embolize (8).

Thoracic Aneurysms

Thoracic aneurysms can be classified into five categories: 1) ascending, 2) transverse, 3) descending, 4) thoracoabdominal, and 5) aortic disruption. In the past, ascending thoracic aneurysms were significantly associated with syphilis, but presently they are most commonly associated with connective tissue diseases, autoimmune disease, and aortitis. Imaging studies such as a CT scan, magnetic resonance imaging, or transesophageal echocardiogram confirm the diagnosis. These aneurysms frequently involve the annulus producing aortic insufficiency. Surgical repair is indicated with subsequent replacement of the involved aorta and repair of the valve as indicated (9).

Transverse thoracic aneurysms are usually produced by atherosclerotic degeneration but may also be secondary to an aortic dissection. It, too, is usually suspected on chest x-ray and confirmed by an imaging study. Surgical repair is extremely complex because the major vessels to the head and upper extremities are involved. Previously, operative intervention was reserved for expanding aneurysms. However, current techniques using hypothermic arrest have reduced operative mortality to approximately 10%, and repair is now recommended (9).

Descending thoracic aneurysms can occur with atherosclerosis, syphilis, trauma, aortitis, infection, or dissection. Again, diagnosis is usually suspected on chest x-ray with an imaging study confirming the suspicion. Enlargement is associated with rupture; therefore surgical intervention is indicated for enlarging or symptomatic aneurysms (10).

Thoracoabdominal aneurysms involve both the thoracic and abdominal aorta to varying degrees. Fortunately these are rare because operative intervention can be technically difficult. Rupture is a cataclysmic event requiring emergent surgical intervention. Otherwise surgical intervention should be attempted only when there is evidence that the aneurysm has significantly enlarged or is compressing adjacent structures. The major complication with surgery is spinal cord ischemia with resultant paralysis. Recent studies with close intraoperative and postoperative monitoring to control central nervous system pressure have demonstrated a remarkable decrease in postoperative paralysis (11).

Aortic disruption or traumatic aneurysms are usually associated with deceleration injury. High-speed motor vehicle crashes, particularly if there is a rollover or ejection from the vehicle, is the most common etiology. A high degree of suspicion is necessary when these mechanisms of injury have occurred. Disruption of the intima and media occur with varying amounts of adventitia comprising the aneurysmal sac; this generally occurs distally to the left subclavian artery because this area of the aorta is relatively fixed. This injury is almost always fatal at the scene. Only 10 to 15% survive to reach the emergency department, and nearly two thirds of these patients will die within the next 6 hours if repair is not accomplished. The chest x-ray usually shows a widened mediastinum, pleural capping, or a left pleural effusion. The aortic angiogram is the gold standard diagnostic test but a transesophageal echocardiogram, CT scan, and magnetic resonance imaging (MRI) have all been used. These patients almost always have significant concomitant injuries requiring aggressive resuscitation and stabilization, and immediate cardiothoracic surgical intervention is essential. If this is beyond the institution's capabilities, an emergency transfer to an appropriate facility may be the patient's only chance for survival (10).

Abdominal Aortic Aneurysms

The incidence of abdominal aortic aneurysms is 30 to 60 per 1000 and is increasing. Rupture of these aneurysms is becoming less common because of early detection and elective surgical repair. Men are affected four times more often than women; infrarenal abdominal aneurysms are the most common type. The patient most likely to present with an aneurysm is an older, male, hypertensive, cigarette smoker. Abdominal aneurysms have been associated with cystic medial necrosis, aortic dissection, Ehler's Danlos, syphilis, change in cholesterol intake, cigarette smoking, and atherosclerosis (12).

Abdominal aortic aneurysms are frequently silent and discovered on routine physical examination or incidentally on imaging studies. Aneurysms increase in size at a rate of approximately 5 mm per year; once they reach 6 cm, there is an exponential increase in aneurysmal rupture (13). The symptoms caused by an expanding or rupturing aneurysm can be extremely variable; any type of back, flank, or abdominal pain can be the presenting complaint. The classic triad for a ruptured aneurysm is back or abdominal pain, decreased blood pressure, and a pulsatile abdominal mass. When abdominal aortic aneurysms rupture through a posterior-lateral tear, the hemorrhage may be contained in the retroperitoneal space for a limited amount of time. Without surgical repair, the retroperitoneal leak will enter the peritoneum resulting in a high rate of mortality.

The diagnosis of a ruptured aortic aneurysm must be suspected quickly, and these patients should have immediate surgical intervention. Diagnostic measures should be reserved for the patient who is stable or in whom there is no palpable mass and no history of an aneurysm. Abdominal films can be suggestive of an aneurysm between 55 and 85% of the time. Radiographic findings include calcification of the aneurysm, soft tissue mass, loss of one or both renal outlines, renal displacement, or loss of properitoneal flank stripe. Ultrasonography has become an extremely useful tool in the diagnosis of an abdominal aortic aneurysm. It is quick, accurate, and relatively inexpensive, and it can be performed in the emergency department at the bedside. The disadvantages of ultrasonography are its extreme dependence on the operator and the possible interference of obesity and overlying bowel gas with the image. The other modalities that can aid in the diagnosis, CT scan and MRI, are suitable only for stable patients. These provide good images of the thoracic as well as abdominal aorta, they are not technician dependent, and they are not affected by bowel gas or obesity. CT scan is the test of choice in the emergency department for diagnosis of the hemodynamically stable patient who has a known aneurysm and a suggestive somatic complaint. It is also useful when there is concern about an inflammatory aneurysm or infection of an aortic graft. MRI gives very-high-quality images, but has the disadvantage of placing the patient in a cylinder for an extended period of time where observation and monitoring may be compromised (14).

The expanding or rupturing abdominal aneurysm is often considered the great masquerader. (See Table 2.) Several studies have established a correlation between mortality and the length of time taken to make the diagnosis of a ruptured aneurysm (15). The elderly patient who presents with back, chest, flank, or abdominal pain should have a careful abdominal examination to assess the presence of an abdominal aneurysm. Immediate management in the emergency department should consist of stabilization with intravenous fluids and blood products and arranging emergent surgical intervention.

TABLE 2

Differential Diagnosis of Abdominal Aortic Aneurysm

Myocardial infarction
Renal colic
Ischemic bowel
Pancreatitis
Perforated ulcer
Appendicitis
Diverticulitis
Biliary colic
Internal hernia

Visceral Aneurysms

Visceral aneurysms are not common and are usually asymptomatic. However, approximately 22% of visceral aneurysms present as surgical emergencies (16). Vague complaints of an abdominal, flank, or pelvic pain precede cardiovascular collapse. Splenic artery rupture occurs disproportionately in pregnant women and can mimic ruptured ectopic pregnancy. Ultrasonography, CT scanning, and MRI can all demonstrate aneurysms in the abdominal vessels. The location, prevalence, and risk of rupture of aneurysms in the visceral vessels are detailed in Table 3.

Peripheral Aneurysms

Peripheral aneurysms are rare. The etiology, presentation and complications of those involving the major vessels, popliteal, femoral, subclavian/axillary and carotid arteries, are presented in Table 4. Aneurysms occurring more distally are usually secondary to trauma or infection. The diagnosis can be made with a duplex Doppler examination; surgical intervention is recommended because embolization or thrombosis can produce ischemia and potential loss of the end organ (16).

Pseudoaneurysms

A pseudoaneurysm, also called a false aneurysm, is a disruption of the arterial wall which allows blood to flow and accumulate outside but adjacent to the artery. There is continuity between the arterial flow and the flow in the cavity created by the disruption in the arterial wall. Pseudoaneurysms can occur at the site of a previous anastomosis (thought to be secondary to infection), or as a result of trauma, needle injury, or

TABLE 3

Visceral Aneurysms

	Location	Lifetime Risk of Rupture
60%	Splenic	2%
20%	Hepatic	20%
5.5%	Superior mesenteric	<<1%[a]
4%	Celiac	13%
4%	Gastric/gastroepiploic	90%
3%	Jejunal/iliac/colic	30%
2%	Pancreaticoduodenal	75%
1.5%	Gastroduodenal	50%
<1%	Renal	3%

[a] Aneurysms of the superior mesenteric artery are complicated by thrombosis rather than rupture.

TABLE 4
Peripheral Aneurysms

Location	Etiology	Presenting Signs	Usual Complication
Extracranial and carotid	Athero-sclerosis, trauma	Palpable, pulsatile, mass	Emboli
Subclavian and axillary	Thoracic outlet, crutch trauma	Distal embolization	Emboli
Femoral and popliteal	Athero-sclerosis	Palpable, pulsatile, mass	Thrombosis

illicit drug use. A duplex Doppler examination can be diagnostic as well as therapeutic for peripheral pseudoaneurysms; several studies have demonstrated a high success rate of closure of the connecting channel if duplex-guided pressure is applied to the area. If this technique is not successful, and the aneurysm is larger than 2 cm, surgery is indicated; otherwise the pseudoaneurysm may be followed with the expectation that it will resolve.

Occlusive Peripheral Vascular Disease

Peripheral Arterial Thromboembolic Disease

Peripheral arterial occlusion can result from either *in situ* thrombosis or embolization. Thrombosis can occur anywhere in the cardiovascular system because of endothelial injury; this may be associated with atherosclerotic lesions or as a result of generalized low-flow states (18). Emboli are most frequently secondary to thrombi but can arise from atheromata, tumor, or foreign bodies. The heart is the source of 85% of thromboemboli; these usually lodge at arterial bifurcations where there is a change in the size of the vessels (17). Atheromatous emboli are usually smaller and consist of cholesterol, calcium, and platelet aggregates which lodge more distally, usually in terminal digits.

Peripheral findings associated with acute occlusion and ischemia can include the five "Ps": pain, pallor, absent pulse, paresthesia, and paralysis. If paralysis and paresthesia occur, the patient has what must be considered limb-threatening ischemia and requires immediate surgical intervention. If the limb is ischemic but viable, the differentiation between embolism and thrombosis should be made because *in situ* thrombosis can be aggravated by attempted embolectomy.

Classically, the patient with an acute embolism will complain of the sudden onset of a cold, painful leg with paresthesia. The patient may have a history of atrial fibrillation, valvular disease, or recent myocardial infarction. Distal embolization can also occur and is usually called the "blue toe syndrome." Patients present with painful, cyanotic toes but have palpable pulses.

Thrombosis frequently occurs in patients with long-standing peripheral vascular disease and established collateral circulation. The patients will give a history of claudication with physical findings suggestive of peripheral vascular disease. The lower extremities will frequently have diminished or absent pulses; hair loss; thickened toe nails; thin, shiny skin; or ulceration.

Diagnostic tests performed in the emergency department should include Doppler examination of the extremities. Flow characteristics (such as the presence of mono-, bi-, or triphasic signals) should be described; and an ankle/brachial index, which will indicate pressure in the extremity, should be documented. Comparison of the contralateral extremity should be made. Diagnosis can usually be made by physical examination; duplex Doppler examination with angiography can be obtained to confirm the diagnosis. The angiogram can help differentiate an embolism from a thrombus; with thrombosis there is frequently diffuse disease with collateral circulation, but with an embolism the blood vessels appear normal except for the area distal to the embolus (19).

The patient's condition should be stabilized in the emergency department. Immediate vascular surgery consultation is imperative. Possible interventions include surgical thrombectomy, bypass grafting, intra-arterial thrombolytic therapy, and percutaneous transluminal dilation. The administration of heparin may be indicated. Treatment of embolic lesions must also focus on identifying and correcting the source of the emboli (20).

Mesenteric Ischemia

Acute mesenteric ischemia occurs when a segment of the vascular supply of the intestines becomes occluded. Embolization to the superior mesenteric artery occurs six times more frequently than thrombosis. The diagnosis of mesenteric infarction is extremely important; failure to make this diagnosis will result in a gangrenous intestine with perforation and significant mortality. The patient presenting with this entity will have severe abdominal pain, usually out of proportion to the findings of physical examination of the abdomen. The patient may have a cardiac source of emboli, and the pain is usually accompanied by bowel emptying which is guaiac positive. Prompt surgical consultation and angiography should be obtained to avoid potentially fatal delays in diagnosis.

Chronic bowel ischemia is a more difficult diagnosis to make because the symptoms are diffuse and less severe. The patient will frequently present with postprandial abdominal pain, cachexia, and diffuse vascular disease (21). Preliminary diagnosis may be supported by a duplex Doppler examination, but an angiogram will be necessary to confirm the diagnosis.

Uncommon Vascular Emergencies

Aortic Enteric Fistula

An aortic enteric fistula can occur in any patient who has had aortic surgery or who has an abdominal aortic aneurysm. A fistula can occur anywhere in the gastrointestinal tract, with 85% occurring at the duodenum (1). About 90% of patients with an aortoenteric fistula complain of gastrointestinal bleeding; 35% present with hematemesis, 30% with melena, and 8% with hematochezia. A small bleed, often called a herald bleed, may occur before continuous bleeding. Aortoenteric fistula is rare, occurring in only 2% of patients with massive gastrointestinal bleeding and a history of aortic surgery (10). There is no completely reliable diagnostic test; upper endoscopy is usually done first, followed by a CT scan, MRI, or an indium-labeled white cell study. All of these may demonstrate inflammation around the aorta, but they do not reveal the fistula. A high clinical suspicion is necessary in patients at risk; if this condition is not recognized, fatal exsanguination will occur.

Mesenteric Venous Thrombosis

This entity should be considered when there are vague digestive complaints and a history of thrombophlebitis or coagulopathy (1). Patients initially present with mild abdominal pain, abdominal distension, and nausea. If not treated, thrombus in the superior mesenteric vein will impede arterial flow to the small bowel, which results in venous gangrene. These patients present with fever and progressive signs of an acute abdomen. CT scans are extremely accurate in confirming this diagnosis. Treatment is long-term anticoagulation.

Phlegmasia Alba Dolens

Phlegmasia is a major venous thrombosis of the thigh and pelvic veins. The patient presents with pain, pitting edema, and blanching of the affected extremity. This condition occurs more frequently in pregnancy and is four times more common on the left side because of the mechanical compression by the right iliac artery. The limb progressively becomes more edematous, and eventually arterial flow becomes obstructed because of the impedance of venous return. Venous gangrene may develop if appropriate intervention is not accomplished. Duplex Doppler examination can aid in this diagnosis (16). Initial therapy should include anticoagulation and leg elevation. If this treatment is not successful, it should be followed by a venous embolectomy; thrombolytics have also been used with this entity.

Subclavian Vein Thrombosis

Subclavian vein thrombosis can occur as a consequence of an indwelling catheter or in association with thoracic outlet obstruction. The patient with thrombosis secondary to an indwelling catheter should have it removed and may or may not be placed on heparin depending on the patient's condition and the degree of edema. The patient with obstructive venous thrombosis, however, will complain of edema of the upper extremity after exertion of the affected limb. Upon examination, the affected arm will be edematous, and frequently has dilated superficial veins and venous congestion (22). Diagnosis can be made with a duplex Doppler examination or a venogram. The patient should be treated with thrombolytics or heparin and surgical intervention several months later to correct the anatomical problem (23).

In summary, vascular emergencies must be recognized rapidly to facilitate appropriate treatment in the emergency department. Hypotension should be managed aggressively with intravenous fluids and blood products; hypertension must be treated with appropriate therapy. Pain should be adequately controlled. Appropriate laboratory tests should be monitored, and when indicated, diagnostic imaging studies should be obtained. In most cases, urgent surgical intervention must be obtained to preserve life or limb.

References

1. Ernst CB, Stanley JC, editors. Current Therapy in Vascular Surgery, 2nd ed. Philadelphia: B.C. Decker, 1991: 335–346.
2. Griffith GL, Todd EP. Acute aortic dissection. South Med J 1985; 78:1487–1493.

3. Slater EE, Desanctis RW. The clinical recognition of dissecting aortic aneurysm. Am J Med 1976; 60:625–633.
4. Moncada R, Demos TC, Churchill R. Detecting disease of the aorta by computed tomography. J Cardiovasc Med 1983; 186–202.
5. Banning AP, Masani ND, Ikram S, et al. Transesophageal echocardiography as the sole diagnostic investigation in patients with suspected thoracic aortic dissection. Br Heart J 1994; 72:461–465.
6. Wiet SP, Pearce WH, McCarthy WJ, et al. Utility of transesophageal echocardiography in the diagnosis of disease of the thoracic aorta. J Vasc Surg 1994; 20:613–620.
7. Semashko DC, Bush HL, Kosovky PA. Preoperative assessment of aortic aneurysms using magnetic resonance imaging. J Cardiovasc Surg 1991; 32:S37.
8. Friedman SA. The evaluation and treatment of patients with arterial aneurysms. Med Clin North Am 1981; 65(1):83–103.
9. Schwartz SI, editor. Principles of Surgery, 6th ed. New York: McGraw-Hill, 1994:903–924.
10. Bergan JJ, Yao JST. Aortic Surgery, WB Saunders Co: Philadelphia, 1989:247–267.
11. Crawford ES, DeNatale RW. Thoraco-abdominal aortic aneurysm: Observation regarding the natural course of the disease. J Vasc Surg 1986; 3:578–582.
12. Auerbach O, Garfinkel L. Atherosclerosis and aneurysm of the aorta in relation to smoking and age. Chest 1980; 78:805–809.
13. Limet R, Skalihassan MD, Albert A. Determination of the expansion rate and the incidence of rupture of abdominal aortic aneurysms. J Vasc Surg 1991; 14:540–548.
14. Gnomes MN, Schellinger D, Hufnagel C. Abdominal aortic aneurysm: diagnostic review and new techniques. Ann Thorac Surg 1979; 27:479–488.
15. Johansen K, Kohler TR, Nicholls SC, et al. Ruptured abdominal aortic aneurysm: The Haborview experience. J Vasc Surg 1991; 13:240–247.
16. Moore WS, editor. Vascular Surgery: A Comprehensive Review, 3rd ed. Philadelphia: WB Saunders, 1991:325–349.
17. Elliott JP, Hageman JH, Szilagyi DE, et al. Arterial embolization: Problems of source, multiplicity, recurrence and delayed treatment. Surgery 1980; 88:833–845.
18. Wall RT, Harker LA. The endothelium and thrombosis. Ann Rev Med 1980; 31:361–371.
19. Rutherford RB, editor. Vascular Surgery, 4th ed. Philadelphia: WB Saunders, 1995:641–668.
20. Fisher DF, Clagett GP, Brigham RA, et al. Dilemmas in dealing with the blue toe syndrome: Aortic versus peripheral source. Am J Surg 1984; 148:836–839.
21. Boley SJ, Sprayregan S, Siegelman SS, et al. Initial results from an aggressive roentgenological and surgical approach to acute mesenteric ischemia. Surgery 1977; 82:848–855.
22. Gloviczki P, Dazmier RJ, Hollier LH. Axillary-subclavian venous occlusion: the morbidity of a non-lethal disease. J Vasc Surg 1986; 4:333–337.
23. Druy EM, Trout HH, Giordano JM, et al. Lytic therapy in the treatment of axillary and subclavian vein thrombosis. J Vasc Surg 1985; 2:821–827.
24. Bergan JJ, Yao JST, editors. Vascular Surgical Emergencies, 1st ed. New York: Grune & Stratton, 1988:203–217.

Disaster Medicine

Neill S. Oster, M.D.

Abstract

The American College of Emergency Physicians defines a medical disaster as occurring when the destructive effects of natural or man-made forces overwhelm the ability of a particular region to meet the demand for health care. The science of disaster medicine is continually improving, and significant progress has been made in defining how to provide a comprehensive response to disaster sites. The management of a disaster involves an activation phase, followed by the implementation and recovery phases. The success of each phase depends on coordinated on-site and off-site communication systems. This paper presents an overview of this new subspecialty and discusses the fundamental components of an effective disaster response. **Key Words:** disaster, mass casualty, critical incident stress management, Federal Emergency Medical Assistance, Federal Response Program.

Disaster Medicine is developing as a subspecialty within Emergency Medicine (1). Although it is still in its infancy, this new subspecialty has begun, in both the domestic and international arenas, to compile the data needed to guide future growth (2–5). This paper provides an overview of disaster planning and discusses the fundamental components necessary for an effective response to a disaster. (See Table 1.)

The scope and diversity of health services, personnel, equipment, and supplies that are required in response to a medical disaster are staggering; an effective response requires a comprehensive, coordinated, multidisciplinary approach. Emergency physicians are ideally suited to coordinate this response. Their training is broad based in both medical and surgical emergencies, and they routinely work under high-volume, stressful conditions. In the hierarchy of emergency medical services (EMS), emergency physicians are clinical coordinators, supervisors, and providers. In the hospital, emergency physicians are triagers, care givers, and regulators of care access. Historically, emergency physicians have coordinated medical disaster responses with government agencies, police and fire agencies, as well with search and rescue workers (3, 6–8).

The Scope of Disaster Medicine

The American College of Emergency Physicians (ACEP) defines a medical disaster as an occurrence ". . . when the destructive effects of natural or manmade forces overwhelm the ability of a given area or community to meet the demand for health care" (9). Consequently, disasters can be described in terms of their "functional impact" on the health care system: This functional impact is determined by the resources in the community, and the community's ability to utilize its resources (1).

Disasters are classified as either natural or man-made. Natural disasters include earthquakes, typhoons, tornadoes, volcanic eruptions, and floods. Man-made disasters include hazardous material incidents; industrial explosions; airplane, train, and bus calamities; acts of terrorism and war. Increasing population concentrations contribute to the occurrence of mass casualties, and medical disasters have become a front page reality. Domestically, the United States has suffered through a multitude of man-made and natural disasters within the past two decades, and the

---

From the Department of Emergency Medicine, Mount Sinai School of Medicine, New York. Clinical Instructor. Address correspondence to Neill Oster, M.D., Elmhurst Hospital Center, Department of Emergency Medicine, 79-01 Broadway, Elmhurst, NY 11373.

TABLE 1
Abbreviations Frequently Used in Disaster Medicine

CDRG	Catastrophic Disaster Response Group
CISM	Critical Incident Stress Management
DMAT	Disaster Medical Assistance Team
DMORT	Disaster Mortuary Team
EMS	Emergency Medical Service
EPA	Environmental Protection Agency
ESF	Emergency Support Functions
FEMA	Federal Emergency Medical Assistance
FRP	Federal Response Plan
HAZMAT	Hazardous Materials
ICS	Incident Command Systems
NDMOC	National Disaster Medical Operations Center
NDMS	National Disaster Medical Systems
NSEP	National Security Emergency Preparedness
OEP	Office of Emergency Preparedness
USAR	Urban Search and Rescue

ernment spends up to an estimated $1 billion ek as a result of natural disasters (10).

The goals of disaster medicine are 2-fold: to vide an efficient and prepared medical re- onse to any type of medical disaster and to pre- nt medical disasters through proper and in- rmed disaster planning. Knowledge gained from nalysis of the experience with catastrophic events has contributed to the formation of medical response teams at the federal, state, and local levels. The basic foundation for effective disaster medical response at any level is detailed planning and preparation with regular drill simulation and critique (11–14).

The Federal Response

An organized federal government response plan to disasters is a relatively new phenomenon (3). The Federal Emergency Management Agency (FEMA) was created by President Carter in 1979. Under FEMA, many disparate disaster and emergency programs were consolidated including the National Fire Administration, Civil Defense, and a variety of insurance programs designed to underwrite otherwise unobtainable property, flood, and earthquake insurance (3, 4, 6). The Federal Response Plan (FRP) was established in April 1992 when the American Red Cross joined resources with the 26 federal agencies in FEMA.

The Federal Response Plan continues to evolve in its efficiency and scope and its ability to respond cohesively to various types of disasters. FEMA is charged with organizing a multiagency disaster response with effective interagency cooperation and communication. In the unstable and chaotic environment at a disaster site, multiple tasks such as medical care, search and rescue, engineering, and hazardous materials disposal must all be coordinated simultaneously. The need for a comprehensive response plan is obvious; without adequate coordination, the situation will be hopelessly complicated by communication problems within and between the various agencies involved at the local, state, and federal levels.

The FRP is an attempt to organize a system of required responders in a disaster. The FRP divides these responders into sections termed emergency support functions (ESFs), which are under the direct supervision of FEMA. FEMA is responsible for deciding which support services are required in a particular disaster and designating a lead agency to oversee the response delivery. In addition to the lead agency, FEMA also identifies other cooperative agencies to assist the lead agency in delivering the response. The 12 identified ESFs and their lead agencies are presented in Table 2. The ESFs and the lead agencies responsible for their deployment in a disaster require many trained personnel who must interact with their counterparts at the state and local community level.

The responsibilities of FEMA and the designated ESFs in a disaster include transporting re-

TABLE 2
Federal Response Plan Emergency Support Functions (ESF)

Function (ESF)	Lead Agency and Telephone
1. Transportation	Department of Transportation 888-279-7718
2. Communications	National Communication System 888-616-1996
3. Public works/engineering	US Army Corps of Engineers 800-249-0326
4. Firefighting	Department of Agriculture 800-424-9121
5. Information/planning	Federal Emergency Management Administration 800-462-9029
6. Mass care	American Red Cross 800-540-2000
7. Resource support	General Services Administration 888-813-5498
8. Health and medical services	Department of Health and Human Services 800-638-0824
9. Urban search and rescue	Federal Emergency Management Administration 800-462-9029
10. Hazardous material	Environmental Protection Agency 800-435-2174
11. Food	Department of Agriculture 800-535-4555
12. Energy	Department of Energy 800-888-7986

sponders to the disaster site, coordinating search and rescue operations, mobilizing and utilizing equipment, and deploying health care providers. Health care providers must be chosen according to the specific needs of the disaster site, for instance, nuclear decontamination requires different expertise than multiple trauma. In addition to special skills, the medical responders must be prepared and equipped to function within the limitations of the disaster environment. The ESF dedicated to addressing health and medical services under the FRP has a total of 16 health-related responsibilities.

Within each ESF, an understanding of all responders' roles and the cooperative deployment and utilization of interagency services is mandatory. The initiation of a federal response requires a request from the state, the primary authority in any disaster response, usually from the governor. The federal response is then activated in continuing support of the state agencies and local agencies already responding to the disaster. Many agencies, offices, and administrative centers are mobilized in a federal disaster response. Most of these are administrative and function to facilitate appropriate assessment and continued response to the needs of the disaster site and community. There is one administrative center which requires specific mention, however: the Incident Command System (ICS). The ICS entails setting up a command center at or near the disaster site which centralizes and coordinates all activities, assignments, and communications under a hierarchal chain of command; the senior individual in the first responders' team assumes the lead role after the disaster site itself has been assessed.

The National Disaster Medical System (NDMS). In 1981 the NDMS was established to provide medical assistance to disaster areas using volunteer medical teams, to evacuate victims, and to provide hospitalization in a nationwide network of hospitals that have agreed in advance to accept disaster victims (15, 16). The NDMS resulted from the efforts of four federal sponsoring agencies: the Department of Health and Human Services, the Veterans Administration, the Department of Defense, and FEMA, in cooperation with the civilian hospital sector.

Disaster Medical Assistance Teams (DMATs) is the term for the volunteer disaster teams which were organized and supported at the state and local level. DMATs are intended to be able to respond within 6 hours to a state's disaster needs or a federal request for assistance. A Level 1 DMAT comprises 35 medical and support personnel who are totally self-sufficient and able to sustain a deployment of up to 2 weeks at a disaster site. These Level 1 DMATs are required to be able to treat and manage up to 250 patients within a 24-hour period and are deployed to assist the local medical system at the disaster site. The first deployment of a DMAT was in 1989 to St. Croix to care for the victims of Hurricane Hugo (8). Presently there are 61 DMATs in various stages of readiness; of these, 21 are considered to be at Readiness Level 1 (3).

Disaster Scene Response

There are three main phases to a disaster response: activation, implementation, and recovery (9). The activation phase involves the initial scene assessment and mobilization of resources. The activation phase contains the crucial and immediate communication and information relays which are needed to provide an adequate and appropriate response to the disaster scene. The first responders to the disaster site are responsible for performing a scene assessment, estimating the extent and type of casualties, surveying the extent of environmental damage, and identifying which routes to the disaster site remain accessible. This information is transmitted to the first responders' medical command so that the correct resources can be deployed. The next step in the activation phase is the establishment of an ICS. This will be the central command center for all communications, tasks, and activities at the disaster scene. The ICS is best located at a site as close to the disaster as environmental conditions and safety considerations permit. The location of the ICS should allow for continual scene assessment. Because disasters are dynamic, changes both in number and severity of casualties and in environmental conditions may be rapid. Attention must be paid to assure the safety of rescue workers.

The implementation phase is the second phase of a disaster and it focuses on victim care. This phase is initiated with the search-and-rescue of victims, which ideally involves both medical and rescue personnel. In many types of disasters, victims must be located and extricated, before receiving medical care. Because of the dangers inherent in this phase, constant communication and surveillance are critical in preventing further casualties at the disaster site. Once the victims are located and extricated by the search-and-rescue process, medical care begins with primary patient assessment and triage.

In situations in which medical resources are limited, prioritization of care to those patients who will most benefit becomes very important. A casualty collection point is established near, but a safe distance from, the disaster site where triage and early medical assistance can be administered. Triage is a process of sorting based on medical need; criteria are used to decide who will receive care and how much care they will receive (17). It must be emphasized that disaster triage principles differ from the triage system used in routine medical situations. In disaster triage, care which is likely to be futile is withheld to conserve limited resources; this allows the most good to be done for the largest number of victims.

There are several disaster triage systems, most using a tagging system (12, 18). In a typical four-category system, patients are classified as severe, moderate, minor, or dead (or expectant). In the severe category are patients who are critical but have a reasonable chance of survival with care; this group receives the highest priority for care and transport. In the moderately injured group are patients whose injuries are relatively stable and who do not need immediate care and transport. In the minor category are the "walking wounded," patients whose injuries will not lead to significant morbidity while they wait for treatment and transport of the two higher categories. In the fourth category are victims who are dead or who have terminal injuries. Triage categorization is a dynamic and ongoing process. It is entirely possible for a patient who is initially triaged as "a walking wounded" to deteriorate; they should then be reclassified into the "moderate" or "severe" category. Disaster triage training is essential to all prehospital personnel and emergency clinicians; rendering selective care is a difficult transition for most emergency medical providers who are trained to perform heroic lifesaving techniques on any and all injured patients.

After triage and initial stabilization of victims, transport to hospitals or alternate medical facilities is accomplished according to medical priority. The ICS monitors all activities of all responders and has a medical command system unit which oversees all medical care and personnel. The need for constant assessment, monitoring, and communication in a disaster can not be overstated. All processes are dynamic, sometimes dramatically so; the structure, organization, and hierarchy of an ICS provide the most efficient use of resources in a disaster.

Recovery is the third phase of a disaster. It involves reassessment of the scene for any missed victims, and subsequent withdrawal of prehospital services and search and rescue personnel. Community, state, or federal agencies may remain at the scene, providing for basic human needs, such as food, clothing, and shelter, in the aftermath of a disaster (19). The recovery stage should also include a debriefing for all involved personnel (10). One purpose of such a debriefing is to improve future response to disasters through review and analysis of operational function. Another reason for debriefing after the disaster is to provide critical incident stress management (CISM) for all responder and rescue personnel; these individuals may or may not be aware of their own need to process the psychological impact of the disaster operation.

CISM has become a prominent topic, especially in the wake of the Oklahoma City bombing (20–22). The post-traumatic stress of a disaster can inflict deep scars on the psyche of anyone involved in a disaster; even on persons considered to be balanced, centered, and emotionally stable. Disaster medicine is now recognizing the need for CISM among all responders to a disaster. Reductions in the post-traumatic stress of a disaster are being achieved by providing CISM on the scene by specially trained teams (20). The CISM program is needed throughout all phases of a disaster and must continue long-term to address the needs of both rescue personnel and victims.

Disaster Planning and Preparedness

Disaster planning and preparedness can limit the extent and scope of human casualties in a disaster. Although many disasters are unpredictable and unpreventable, there are potential disasters for which vulnerable regions can prepare. Earthquakes more frequently occur along fault lines; hurricanes hit specific coastal areas with regularity; tornado- and flood-prone areas are well known. Regional planning for likely disasters is now common practice, and preparedness for multivariant disasters is possible.

All hospitals are required by the Joint Commission on Accreditation of Health Organizations to have a written disaster plan which is tested at least twice yearly. A comprehensive hospital disaster plan begins with a community assessment to identify likely disaster scenarios and the resources necessary for an effective response. Specific procedures to activate the plan and to notify key individuals must be developed. Mechanisms which allow the call-in of staff for night or weekend responses must be created. Every department in the hospital must determine which, if any, usual functions must continue and which can be suspended to allow staff, equipment, and other resources to be reassigned to caring for disaster victims. Whenever possible, people should be as-

TABLE 3

Elements of a Hospital Disaster Plan

1. Assessment of health/medical needs
2. Surveillance of health care issues
3. Acquisition and distribution of medical care and support personnel
4. Acquisition and distribution of medical and communications equipment and supplies
5. Evaluation of patients
6. In-hospital care of patients
7. Food/drug/medical device safety
8. Worker health/safety
9. Radiologic monitoring
10. Chemical monitoring (hazmats)
11. Biologic monitoring
12. Mental health assessment
13. Development and dissemination of public health information
14. Vector control
15. Water safety, waste-water and solid-waste disposal
16. Victim identification/mortuary services

signed to tasks or to work in areas with which they have some familiarity. Every individual employee in the hospital must know their role; frequent drills are critical to ensure universal readiness.

The hospital plan must address both external and internal disasters. Contingency plans must be developed to deal with the loss of power, heat, water, telephone, and other communication systems within the hospital, as well as partially and completely structural and environmental calamities. Evacuation routes and procedures must be included for each contingency. Because a single event can have an impact on the hospital and other structures, the internal disaster plan must be able to work in conjunction with the external plan and with the local, state, and federal plans (23). Table 3 presents the important features of a hospital disaster plan.

The comprehensive hospital disaster plan incorporates many of the principles of disaster response already discussed. A high degree of coordination and excellent communication are essential: an internal incident command system with specific responsibility and authority, including interfaces with EMS, police, and community agencies. Auf der Heide, in his book, “Community Medical Disaster Planning and Evaluation Guide,” provides strong evidence supporting the need for interagency planning between hospitals and community agencies (24). His analysis of numerous disasters reveals that hospitals often fail to prepare for substantive problems that develop in disasters and that proper planning could avoid significant complications which result from an ineffective disaster response.

Conclusion

The science of disaster medicine is evolving, and significant progress has been made in understanding the methodologies for providing an organized response. There is an increased awareness of the need for a multidisciplinary approach to disasters that can effectively mobilize needed resources in a coordinated effort. In addition, disaster plans must recognize the various types of potential disasters and be flexible to accommodate each contingency. Through proper planning and preparation, disaster responses will continue to improve in the future, reaping benefits in decreased pain, suffering, and loss of life in both victims and rescue personnel.

References

1. Koenig K, Dinerman N, Kuehl A. Disaster nomenclature: A functional impact approach: The PICE system. Acad Emerg Med 1996; 3:723–727.
2. Orient J. Disaster preparedness: An international perspective. Ann Intern Med 1985; 103:937–940.
3. Pretto E, Safar P. National medical response to mass disasters in the United States. JAMA 1991; 266:1259–1262.
4. Roth P, Gaffney J. The federal response plan and disaster medical assistance teams in domestic disasters. Emerg Med Clin North Am 1996; 14:371–382.
5. Noji E, Kelen G, Armenian H, et al. The 1988 earthquake in Soviet Armenia: A case study. Ann Emerg Med 1990; 19:891–897.
6. Geehr E, Salluzzo R, Bosco S, et al. Emergency health impact of a severe storm. Am J Emerg Med 1989; 7: 598–604.
7. Schultz C, Koenig K, Noji E. A medical disaster response to reduce immediate mortality after an earthquake. N Engl J Med 1996; 334:438–444.
8. Roth P, Vogel A, Key G, et al. The St Croix disaster and the National Disaster Medical System. Ann Emerg Med 1991; 20:391–395.
9. American College of Emergency Physicians: Disaster Planning and Management for the Emergency Physician. Emmitsburg, MD: Federal Emergency Management Agency Publication; 1983.
10. Society for Academic Emergency Medicine Disaster Medicine White Paper Subcommittee. Disaster medicine: Current assessment and blueprint for the future. Acad Emerg Med 1995; 2:1068–1075.
11. Cowan M, Cloutier M. Medical simulation for disaster casualty management training. J Trauma 1988; 28:S178–S182.
12. Paris P, Stewart R, Pelton G, et al. Triage success in disasters: Dynamic victim-tracking cards. Am J Emerg Med 1985; 3:323–326.
13. Porter R. Learning it by living it: Bringing realism to EMS training. J Emerg Med Serv 1987; 12:39–41.
14. Waeckerle J. Disaster planning and response. N Engl J Med 1991; 324:815–821.
15. Mahoney BD. Disaster medical services. In: Tintinalli, JE, Ruiz E, Krome RL, editors. Emergency Medicine a Comprehensive Study Guide, 4th ed. New York: McGraw Hill, 1996:20–25.

16. Haynes B, Emmel A. Role of a hospital team at an industrial explosion. Am J Emerg Med 1988; 6:260–265.
17. Bissell RA, Becker BM, Burkie FM Jr. Health care personnel in disaster response. Emerg Med Clin North Am 1996; 14:267–288.
18. Kennedy K, Aghababian RV, Gans L, Lewis Cp. Triage: Techniques and applications in decisionmaking. Ann Emerg Med 1996; 28:136–144.
19. Glittenberg J. Socioeconomic and psychological aspects of disasters. Prehosp Disaster Med 1989; 4:21–30.
20. Mitchell J, Everly G (eds). Critical Incident Stress Debriefing: An Operations Manual For the Prevention of Trauma Among Emergency Service and Disaster Workers. Baltimore: Chevron Publishing, 1993.
21. Burkle FM. Acute-phase mental health consequences of disasters: Implications for triage and emergency medical services. Ann Emerg Med 1996; 28:119–128.
22. Mallone S, Shariat S, Stennies G, et al. Physical injuries and fatalities resulting from the Oklahoma City Bombing. JAMA 1996; 276:382–387.
23. Lewis CP, Aghababian RV. Disaster planning Part I: Overview of hospital and emergency department planning for internal and external disasters. Emerg Med Clin North Am 1996; 14:439–452.
24. Auf der Heide E. Community Medical Disaster Planning and Evaluation Guide. Dallas: American College of Emergency Physicians Publication, 1995: IX.

Severe Head Injury:

Prehospital and Emergency Department Management

SALVATORE SILVESTRI, M.D.[1] AND SUSAN ARONSON, M.D.[2]

Abstract

Head trauma causes approximately 75,000 deaths each year in the United States. Both hypoxia and hypovolemia are individual predictors of poor outcome in the patient with severe head trauma. Management begins in the field and is focused on ensuring oxygenation and maintaining a blood pressure that supports cerebral perfusion. In the trauma center, intracranial pressure monitoring may be helpful in guiding the management of increased intracranial pressure. Mannitol, given in intermittent bolus infusions, is the therapy of choice for increased intracranial pressure. Hyperventilation has been shown to decrease cerebral perfusion and should be avoided; it is a temporizing procedure that is reserved for those cases that demonstrate signs of increased intracranial pressure pending initiation of other therapies. **Key Words:** head trauma, hyperventilation, mannitol, intracranial pressure, cerebral perfusion pressure, emergency medical services.

TRAUMA IS THE LEADING CAUSE of death in the United States in people younger than 40 years of age. Head trauma, in particular, is the leading cause of death among people younger than 24 years of age (1). There are 150,000 deaths caused by trauma each year in the United States, of which 50% are caused by fatal head injuries. The most common cause of head injuries is motor vehicle accidents (2). The annual incidence of head injury in the United States is about 200 cases per 100,000 people, with a peak occurrence in males aged 15 to 30 years (3, 4). Severe head injury is defined by a Glasgow Coma Scale Score (GCS) of less than or equal to 8 (Table 1). Approximately 120,000 severe head injuries occur per year in the United States, and about half of these patients arrive at the hospital alive. Of these, about half have elevated intracranial pressure (ICP) and are in need of aggressive resuscitation to minimize disability (5).

Management of patients with severe head injury often requires multiple interventions. However, medical and surgical practices are at times based on opinion and practice experience rather than scientific evidence, which results in a significant variation in the care provided by various trauma centers. In response to this situation, a multidisciplinary task force was recently assembled by the Brain Trauma Foundation to critically review the literature and to make evidence-based recommendations on the management of patients with severe head injury (6). This paper presents the controversies related to caring for patients with severe head injury and provides an update on current management recommendations.

Prehospital Considerations

Prehospital management of the patient with a severe head injury generally follows protocols provided to emergency medical technicians (EMTs) and paramedics (EMT-Ps) in a Basic Trauma Life Support (BTLS) course or its equivalent (7). Prehospital providers are taught to perform a careful scene assessment upon arrival to identify potential dangers to both the rescuers and to the patient. The assessment also includes notation of the mechanism of injury, the number

---

From the Department of Emergency Medicine, Mount Sinai School of Medicine. [1]FACEP, Clinical Assistant Professor; [2]FACEP, Clinical Assistant Professor. Address reprint requests to Salvatore Silvestri, M.D., Department of Emergency Medicine, Mount Sinai School of Medicine, Box 1149, One East 100th Street, New York, NY 10029.

TABLE 1
Glasgow Coma Scale

Eye Opening	
Opens spontaneously	4
Opens eyes to verbal command	3
Opens eyes to pain	2
Does not open eyes	1
Verbal Response	
Alert and oriented	5
Converses, but disoriented	4
Speaking, but nonsensical	3
Moans or makes unintelligible sounds	2
No response	1
Motor Response	
Follows commands	6
Localizes pain	5
Movement or withdrawal to pain	4
Abnormal flexion (decorticate)	3
Abnormal extension (decerebrate)	2
No response	1
	3–15

of patients involved, and the need for additional help. Patient care at the trauma scene begins with a primary survey which involves an evaluation of the airway, while maintaining cervical spine control, and assessment of the level of consciousness. Breathing and circulation are assessed while simultaneously determining the need for critical interventions such as endotracheal intubation, sealing sucking chest wounds, needle decompression of a tension pneumothorax, and stabilization of a flail chest. Next, there is a brief examination of the abdomen, pelvis, and extremities. Notation should also be made of the patient's GCS, especially in all patients with head injury. The GCS has been validated as a valuable aid in assessing prognosis and in following clinical status in managing patients with head injury. Vital signs, a detailed head-to-toe evaluation, a past medical history, and intravenous access are often best obtained during transport, especially in critically ill patients.

Transport Decision

The overall goals of prehospital management of patients with severe head injuries include rapid recognition and correction of life-threatening conditions, prevention of secondary brain insults, and immediate transportation to the closest appropriate facility, which in the patient with head injuries must include the availability of neuroimaging and neurosurgical resources. Smith et al. (8) demonstrated that patients treated in trauma centers had significantly less mortality than in nontrauma centers. Many emergency medical systems (EMS) operate under preestablished trauma transport protocols. Commonly accepted criteria for transport to a trauma center include severity of injury, a respiratory rate <10, systolic blood pressure <90 mm Hg, a GCS score ≤12, and the mechanism of injury, such as penetrating wounds to the head, neck or torso, amputations, paralysis, or ejection from a motor vehicle.

Field Airway Considerations

Ensuring a patent airway is the highest priority in resuscitation, because hypoxia has been directly correlated with poor outcome in trauma, particularly in head trauma (9). The airway must be secured and maintained throughout transport, and all airway maneuvers must be performed while simultaneously maintaining cervical spine immobilization. Patients with severe head injuries are usually unable to adequately protect their airways, which makes intubation an important consideration. There are several controversies pertaining to the issue of field intubation which include whether patients with severe head injuries should be intubated in the field and, if so, by what method.

The issue of whether field intubation should be performed is a function of transport time, the patient's oxygenation status and clinical evidence of transtentorial herniation (see Table 2). The "golden hour" of trauma begins from the moment of injury; EMS providers could be described as operating within a "platinum 10 minutes," which is the ideal time allotted for transport to the trauma center. It can be argued that any delay in transport, as may occur to successfully accomplish intubation, may result in a critical delay to definitive care; however, it has been reported that prehospital endotracheal intubation is associated with a decreased incidence of hypoxia-related secondary brain insults (9). In general, intubation is recommended in the field if it is utilized to prevent or treat hypoxia, provided that it does not significantly delay transport. Conversely, if hypoxia can be prevented without intubation, and the transport time is short, field intubation probably is not necessary.

The optimal method of intubating patients with severe head injuries in the field is another unsettled issue. Options for emergency airway procedures include blind nasotracheal intubation, oral endotracheal intubation with or without sedative/neuromuscular blockade, and bag-valve-mask-assisted ventilation. The success rate for field nasal intubation is equivalent to that of field oral intubation (10). Every airway procedure performed in the field carries a risk of cervical spine movement; however, although cervical spine movement has been demonstrated to occur during emergency airway procedures (11), studies reveal that the risk of spinal cord injury secondary to oral intubation is low (12, 13). The emergency airway procedure of choice in the patient with severe head injuries must optimize intubation conditions, while minimizing the adverse effects of intubation. The ultimate choice should be determined by the skill and expertise of the prehospital provider, the clinical presentation of the patient, and the specific protocols within EMS.

Field Breathing/ Ventilation Considerations

Intubated patients should receive 100% oxygen, and nonintubated patients should receive supplemental oxygen via a non-rebreather mask at 12 to 15 L/min. In systems that carry pulse oximeters, the target goal is to maintain the oxygen saturation at 100% throughout the prehospital course. Chestnut et al. (14) demonstrated that prehospital hypoxia (defined by apnea/cyanosis in the field, or a $paO_2 < 60$ mm Hg by arterial blood gas analysis) was an independent variable predictive of increased morbidity and mortality from severe head injury.

Circulation Considerations

Similar to the detrimental effects of hypoxia, hypotension is a critical factor related to the morbidity and mortality of patients with head injuries (14). Prehospital hypotension, defined as a single observation of a systolic blood pressure <90 mm Hg, has been found to be an independent predictor of outcome. Patients with a single episode of hypotension have twice the mortality, and increased morbidity, compared with matched patients without hypotension (14).

Blood pressure in the field should be monitored closely to avoid hypotension (SBP <90 mm Hg) and correct it immediately. Generally, intravenous crystalloid administration has been the mainstay of prehospital treatment of hypotension. On the other hand, a study by Vassar et al. (15) showed that prehospital administration of hypertonic (7.5%) saline to a subgroup of patients with severe head injuries resulted in improvement in survival-to-discharge. In this prospective, randomized, placebo-controlled, multicenter trial, 250 cc of 7.5% saline (with and without 6% and 12% dextran 70) was compared with 250 cc of lactated Ringer's in patients with multiple trauma who had a systolic blood pressure >90 mm Hg. *Post hoc* analysis of the severe head injury subgroup revealed a statistically significant improvement in outcome in the hypertonic-saline group. In addition, the prehospital administration of hypertonic saline was shown to significantly improve blood pressure during helicopter transport compared with lactated Ringer's (15). At the present time the role of hypertonic saline remains unclear; however, it may be reasonably considered in the management of patients with severe head injuries who have hypotension.

Other Prehospital Treatment Considerations

A potential pitfall in the management of the patient with severe head injuries is to assume that altered mental status is due solely to the trauma. Consideration must be given to the reversible causes of altered mental status which include hypoglycemia, hypoxia, and drug toxicity. Although it is common practice to administer 50 mL of a 50% dextrose solution in the field to any patient with an altered level of consciousness, this “routine” use of dextrose should be more carefully considered in patients with severe head injuries. In one study of cerebral metabolism in patients with severe head injuries administration of glucose resulted in increased cerebral lactate production (14). In a retrospective study of patients admitted to a trauma center with a GCS score of ≤8, an elevated serum glucose was associated with poorer clinical outcomes (i.e., persistent vegetative state or death) (15). Young et al. (18) demonstrated that patients who had the highest peak admission 24-hour serum glucose levels had the worse 18-day neurologic outcome in a study of patients with brain injuries. They concluded that hyperglycemia is a physiologic response that is associated with severe head injury, that it provides prognostic information, and may aggravate ischemic brain insults. It is recommended for EMS systems to utilize rapid glucose tests to assess the prehospital glucose levels and to avoid the unnecessary administration of dextrose in patients with severe head injuries. Mannitol, which is the treatment of choice for elevated intracranial pressure (ICP), has not been well studied in the prehospital literature. In one prospective, randomized, double-blind (19), placebo-controlled clinical trial comparing the hemodynamic effects of mannitol, Sayre et al. demonstrated that the prehospital administration of 1.0gm/kg of mannitol in patients with head injuries was not associated with any significant change in systolic blood pressure or pulse rate. This study does not support the routine prehospital use of mannitol in all patients with head injuries, but it does support that mannitol can be used without adverse sequelae.

Emergency Department Management

The initial approach to the patient with severe head injury upon arrival at the Emergency Department (ED) follows well-described pathways (see Table 3). Resuscitation, including brain-specific interventions, occurs simultaneously with the assessment. Identification of the factors predictive of poor outcome may be helpful in directing management and minimizing morbidity and mortality. These factors include hypotension, hypoxemia, or hypercarbia, abnormal motor response, impaired or absent eye movements or pupil light reflexes, an intracranial hematoma, or an elevation of intracranial pressure to more than 20 mm Hg (20). Brain injury is a continuum that begins at impact. Many secondary insults that enhance the initial damage occur during the ensuing hours and days. The indications for initiating ICP monitoring and for initiating therapies to lower ICP depend on the patient's clinical presentation, head computed tomography (CT) findings, and resources available. ICP monitoring is a useful tool in recognizing early increases in pressure and a guide to therapeutic interventions, which will be presented below.

When deciding on the optimal approach to managing the airway in the patient with severe head injury, the emergency physician must consider the relationship among airway maneuvers, systemic hemodynamic parameters, and ICP. The approach must allow for rapid insertion of an endotracheal tube while minimizing the risks of significant fluctuations in arterial blood pressure and ICP. In addition, because patients who present to the ED are assumed to have a full stomach, the airway procedure chosen must be one that minimizes the risk of aspiration. Many experts consider rapid sequence intubation as the emergency airway procedure of choice. Rapid sequence intubation (RSI) refers to a specific method of inducing motor paralysis and unconsciousness, through the near simultaneous administration of a neuromuscular blocking agent and a potent sedative, for the purpose of facilitating endotracheal intubation with optimal protection against aspiration of stomach contents by the unfasted patient (21). In the setting of head trauma, this procedure must be done with in-line cervical immobilization. Specific recommendations for performance of a RSI in patients with severe head injuries are outlined in Table 4.

The patient with severe head injuries usually undergoes episodes of agitation and combativeness, both of which tend to increase ICP. Therefore, as first-line treatment for the prevention of increases in ICP, analgesics and sedatives should be used. These agents should be short acting and are usually narcotic analgesics such as fentanyl, and/or a benzodiazepine such as midazolam. These agents help patients to tolerate diagnostic and therapeutic procedures without unacceptable agitation or intracranial hypertension. Use of these agents is contraindicated in the hypovolemic, hypotensive patient.

Once the airway is secured and the patient is hemodynamically stabilized, consideration is

TABLE 2

Signs of Transtentorial Herniation[a]

Clinical evidence of intracranial hypertension
  1. Unilateral or bilateral pupillary dilation
  2. Asymmetric pupillary reactivity
  3. Motor posturing
  4. Progressive neurologic deterioration

---

[a] Not attributable to extracranial explanations.

TABLE 3

Emergency Department Approach to the Patient with Severe Head Injuries

---

I. Primary survey: assessment of ABC's
  A. Airway assessment with cervical spine control
  B. Breathing assessment
  C. Circulatory assessment with bleeding control
  D. Disability assessment
    1. Brief neurologic evaluation
    2. Glasgow Coma Scale
    3. Pupillary response
  E. Exposure
II. Resuscitation (takes place simultaneously with the primary survey)
  A. Oxygen and ventilation: Intubation as needed
  B. Shock management
    1. IV lines
    2. Ringer's lactate
    3. Consider hypertonic saline (7.5%)
  C. Urinary and gastric catheters
    1. Foley (after rectal)
    2. Gastric tube (orally if severe midface trauma)
  D. Monitoring
    1. Oxygen saturation
    2. Capnography (optional)
    3. Cardiac
    4. Blood pressure
  E. Roentgenograms/CT scan
  F. Consider need for transfer
III. Secondary survey: head-to-toe evaluation
  A. AMPLE history (see text) and mechanism of injury
  B. Head-to-toe examination (including back)
IV. Definitive care (see Table 4)
V. Reevaluate/reconsider transfer

given to diagnostic modalities (see Table 5). Without question, all patients with severe head injuries need a CT scan. The only question is the timing of the scan. In the presence of clinical signs of transtentorial herniation or progressive neurologic deterioration, the CT scan should be obtained immediately. In the absence of clinical signs of herniation, CT scanning can be delayed, e.g., for the performance of a diagnostic peritoneal lavage (DPL), but should still be done ideally within 30 minutes of ED arrival. If a surgical lesion be identified on the CT scan, the patient should be immediately transported to the operating theater, where the DPL can be performed while the intracranial compartment is explored.

The use of neuromuscular blockade is also helpful in managing patients with severe head injuries as well as treating intracranial hypertension (ICH). Neuromuscular blockade should be considered in any patient whose transportation, management, or diagnostic imaging is complicated by uncontrolled agitation or combativeness. The paralytic agents used should be short acting to allow for repeat neurologic examinations. It has been reported that prolonged use of prophylactic neuromuscular blockade is associated with

TABLE 4

Recommendations for Rapid Sequence Intubation in Patients with Severe Head Injuries

1. Prediction of difficult airway
   a. Assess patient's anatomy for intubation difficulties, e.g., short, fat neck
   b. Assess potential traumatic causes of airway disruption, e.g., severe facial and/or neck trauma
2. Preoxygenation
   a. 100% oxygen for 5 minutes
   b. Begin in prehospital phase
   c. Avoid positive pressure ventilation ("no bagging")
3. Preparation
   a. Drugs (have all appropriate doses drawn up)
   b. Equipment (assure all is functional; surgical airway set-up at bedside)
4. Premedication (2–3 minutes before paralysis)
   a. Vecuronium (0.01 mg/kg IV)
   b. Lidocaine (1.5 mg/kg IV)
   c. Fentanyl (3–5 μg/kg IV)
5. Sedation
   a. Thiopental (3–5 mg/kg IV; 0.5–1.0 mg/kg IV if hypotensive)
6. Paralysis
   a. Succinylcholine (1.5 mg/kg IV)
   b. Application of cricoid pressure (Sellick's maneuver)
7. Intubation with in-line cervical immobilization
8. Confirm endotracheal tube placement and ventilate
   a. End-tidal CO_2
   b. Oxygen saturation
   c. CXR
9. Consider longer term neuromuscular blockade and sedation

TABLE 5

Emergency Department Management of Severe Head Injury

The following approach is recommended for a patient with head injuries who presents to the Emergency Department with a GCS score ≤ 8.

I. Initial approach
  A. Follow approach (presented in Table 3)
  B. Systemic resuscitation is first priority
  C. Neurosurgical consultation early
II. Airway approach
  A. Oral endotracheal intubation with in-line cervical immobilization
III. Breathing approach
  A. Oxygenation
    1. Maintain oxygen saturation at 100%
    2. Hypoxemia ($paO_2 < 60$ mm HG) must be avoided, and immediately corrected if it occurs
  B. Ventilation
    1. Maintain paO_2 at 35 mm Hg
    2. Avoid hyperventilation ($paO_2 \leq 25$ mm Hg)
IV. Circulation approach
  A. Restoration of circulating volume
    1. Intravenous crystalloid (lactated Ringer's) resuscitation
    2. Blood administration as needed
  B. Maintenance of adequate blood pressure
    1. Hypotension (SBP < 90 mm Hg) must be avoided and immediately corrected
    2. Administer hypertonic saline (250 cc of 7.5% NaCl) as the initial resuscitation fluid in hypotensive patients
V. Herniation approach
  Patients must be monitored closely for clinical evidence of transtentorial herniation (see Table 2)
  A. Presence of clinical signs of herniation (i.e., not attributable to extracranial causes); proceed in order of 1 through 4 (Item 4 is last intervention.)
    1. Consider sedation (short-acting agents)
      a. Benzodiazepines (midazolam)
      b. Barbiturates (thiopental)
      c. Narcotics (Fentanyl)
    2. Consider paralysis (nondepolarizing agents)
      a. Vecuronium, 7–10 mg IV perfusion (0.1 mg/kg)
      b. Rocuronium, 40–70 mg IV perfusion (0.6–1.0 mg/kg)
    3. Consider mannitol 0.25–1.0 g/kg IV bolus provided patient is euvolemic
      a. Avoid hypovolemia by fluid replacement
      b. Maintain serum osmolarity < 320 mOsm
    4. Consider hyperventilation ($paCO_2 \leq 25$ mm Hg)
      a. A temporizing measure only
      b. Indicated for longer periods if increased ICP is refractory to sedation, paralysis, CSF drainage (if ICP catheter in place), and mannitol
VI. Diagnostic modalities
  A. Assess urgency of CT scan (head)
    1. Obtain immediately if signs of herniation exist
    2. Delayed (but ideally within 30 min of ED arrival) if no signs of herniation
    3. Direct patient transport to operating theater if surgical lesion noted on CT scan

TABLE 5
Continued

- VII. ICP monitoring indications
  - A. Head CT scan normal (with GCS ≤ 8) plus two or more of the following:
    - 1. Age > 40 years
    - 2. Unilateral or bilateral posturing
    - 3. SBP < 90 mm Hg
  - B. Abnormal CT scan (with GCS ≤ 8)
- VIII. Other brain-specific modalities
  - A. Barbiturate therapy
    - 1. High-dose therapy in hemodynamically stable patients with elevated ICP refractory to maximal medical and surgical ICP-lowering therapy
    - 2. Not recommended prophylactically
  - B. Steroids are not indicated
  - C. Anticonvulsant use
    - 1. Phenytoin is effective in preventing early post-traumatic seizures
      - a. Prophylactic anticonvulsant use is not recommended for preventing late (more than 1 week after injury) post-traumatic seizures
      - b. Prevention of early post-traumatic seizures has not been shown to improve outcome

a longer intensive care unit (ICU) course, a higher incidence of pneumonia, and a trend toward more frequent sepsis without providing improvement in outcome (6).

Cerebral Perfusion Pressure and ICP Monitoring

Cerebral perfusion pressure (CPP) is the physiologic variable that defines the pressure gradient for cerebral blood flow (CBF). It is the critical determinant of cerebral ischemia which is one of the most important factors affecting neurologic outcome after brain injury. The CPP is the product of the mean arterial pressure minus the ICP, thus monitoring of the ICP is a necessity for CPP assessment. It is generally accepted that CPP is best maintained between 70 and 80 mm Hg. Under normal conditions, the brain is able to tightly control CBF through the process of autoregulation. Autoregulation is often lost in severe brain injury. A low CPP may jeopardize a region of the brain with preexisting or borderline ischemia, whereas a high CPP may result in progressive cerebral edema and neurologic deterioration (22). Robertson et al. (23) showed that patients with a reduced CBF had a poorer outcome than patients with a normal or raised CBF and that reduced CBF remained significantly associated with an unfavorable neurologic outcome. However, there is no direct relationship between CBF and ICP. In fact, increasing blood pressure to maintain CPP, which will maintain CBF, may or may not increase ICP. It seems likely that maintaining the CPP between 70 and 80 mm Hg will enhance perfusion to ischemic areas of a brain after severe total brain injury, but studies are needed to show conclusively that this improves outcome.

ICP monitoring is used to facilitate maintenance of an adequate CPP. The ICP is normally 0 to 10 mm Hg, and, in general, an ICP greater than 15 to 25 mm Hg is an indication to initiate therapy to lower the pressure. In patients with severe brain injury, strong consideration is given to ICP monitoring; however, there are no definitive prospective studies demonstrating improved outcome in those patients monitored versus those who are not. ICP monitoring is recommended in patients with severe head injury who have a head CT which demonstrates edema, hemorrhage, hematomas, contusions, or compressed basal cisterns. It is also recommended in those patients with brain injuries who have a normal head CT but who have at least two of the three features that have been associated with ICH: Age greater than 40 years, unilateral or bilateral posturing, and a systolic blood pressure of less than 90 mm Hg (24). When less than two of these features are present and the patient has a normal head CT, the risk for developing ICH is low and ICP monitoring is probably not indicated (6).

In general, treatment of an increased ICP should be initiated at an upper threshold of 20 to 25 mm Hg (6). Studies by Marmarou et al. (25) and Eisenberg et al. (26) suggest that there are improved outcomes when the ICP is maintained at less than 20 mm Hg. Multiple studies report an association of elevated ICP with an increased mortality and chronic disability (24, 26, 27). Outcome is likely to be associated with both the degree of elevation of the ICP as well as its persistence (26). Interestingly, Miller et al. (27) reported that the predictive value of an increased ICP depended on the underlying pathology. In patients with diffuse brain injury any increase in ICP above 10 mm Hg was associated with a poor neurologic status and a worse outcome, whereas in patients with mass lesions, an increase in the ICP was not predictive of poor outcome until it was more than 40 mm Hg (27). They concluded that in traumatic brain injury, the ICP itself was a cause of neurological deterioration when it increased to the point of impairing cerebral perfusion. However, the ICP is only one of several indicators of the severity and extent of brain damage which is caused by multiple factors including the primary injury, tissue swelling, and vascular dilation or congestion.

Hyperventilation

The role of hyperventilation in the management of brain injury has been reassessed recently. In the past, hyperventilation, maintaining a pCO_2 at less than 25, was a mainstay of treatment in patients with severe brain injury (29). It was considered an effective means of maintaining a low ICP and reversing central nervous system acidosis (28), but its use and benefit have become controversial. Hyperventilation leads to an initial decrease in the ICP by causing an immediate cerebral vasoconstriction with a resultant increase in cerebral vascular resistance and a decline in CBF (30). However, there is evidence that cerebral anoxia occurs as the result of the cerebral vasoconstriction (31). It has been demonstrated that CBF is significantly decreased in the first 24 hours after severe brain injury, particularly in the first few hours (32) and because CBF is reduced even further with hyperventilation, hyperventilation places the patient with brain injury at additional risk for cerebral ischemia (33, 34). THAM (trimethamine) is a buffer which enters the CSF compartment reducing cerebral acidosis and has shown promise in overcoming some of the disadvantages and reversing the adverse effects of hyperventilation in patients, although further studies are needed (28, 35).

Hyperventilation should be avoided in the absence of uncontrolled increases in ICP. Hyperventilation therapy is presently only recommended as a temporizing measure in patients with signs of increased ICP in whom mannitol therapy is either not available or has been ineffective (see below). Especially during the first 24 hours, CBF is often already reduced and hyperventilation may further impair cerebral perfusion (6). However, it is still unclear whether short episodes of hyperventilation during the first 24 hours after injury is deleterious. It is also unclear whether patients who spontaneously hyperventilate after severe brain injury should be controlled (6).

Mannitol

Mannitol, an osmotic diuretic, is effective in controlling raised ICP after severe head injury. It can reduce ICP by 26% or more within 5 minutes of administration and is considered a mainstay of treatment in patients with severe head injuries who have suspected or raised ICP (36). Mannitol is administered in the dose range of 0.25 to 1 g/kg. There are data suggesting that intermittent boluses are more effective than continuous infusions (6). In a study by Mendelow et al. (37) mannitol consistently reduced ICP and increased CPP and CBF by 10 to 20 minutes after infusion. There are data which suggest that there may be little benefit in using mannitol if the CPP is more than or equal to 70 (38). Ideally, mannitol is given once ICP monitoring is in place, although therapy should not be delayed in patients showing signs of increased ICP. ICP monitoring can help avoid the deleterious effects of over-administration of mannitol (39). When using mannitol, care should be taken to maintain the patient in a euvolemic state by fluid replacement and to keep the serum osmolarity below 320 mOsm to decrease the chances of renal failure (6).

Mannitol has two proposed mechanisms of action. One is an immediate but transient plasma-expanding effect leading to improved cerebral perfusion as the result of a reduced hematocrit (27), reduced blood viscosity (36, 41), and increased CBF with improved oxygen delivery (36, 37, 40, 42, 43). The second mechanism by which mannitol benefits the patient with severe brain injury is an osmotic effect which is delayed for 15 to 30 minutes while gradients between plasma and cells are established (6). This effect lasts 90 minutes to several hours (44), possibly depending on the dose of mannitol used (45). Marshall et al. (45) concluded that smaller and more frequent doses are as effective in reducing the ICP while avoiding the risk of osmotic disequilibrium and severe dehydration. Because mannitol is excreted in the urine, there is a risk of acute renal failure secondary to acute tubular necrosis if large doses are administered.

After either multiple doses or continuous infusions, mannitol may exacerbate ICP by increasing brain swelling, the so called “rebound effect” (44). This increase in vasogenic edema may be caused by accumulation of mannitol in the injured tissue (46). Long-term use of mannitol also places the patients at risk for changes in fluid balance, electrolytes, and serum osmolarity (39). However, when administering mannitol, it seems that repeat boluses rather than a continuous infusion may avoid these complications. Mannitol has been shown to be useful in the patient with multiple injuries who has coexistent severe head injury and hypovolemic shock caused by systemic injuries. Israel, et al. (43), using a canine model for elevated ICP and hemorrhagic shock, compared mannitol with normal saline. They found that mannitol lowered the ICP, improved CPP, and despite vigorous diuresis, did not compromise cardiovascular stability.

Barbiturates

High-dose barbiturates are recommended in hemodynamically stable patients with severe head injuries who have ICH that is refractory to maximal medical and surgical ICP-lowering therapy (6, 26). They are not recommended prophylactically (26, 47). Barbiturates can lower the ICP and therefore potentially improve outcome, assuming that controlling the ICP decreases mortality and morbidity. However, there are potential complications of treatment, including hemodynamic instability, which make intensive care monitoring necessary.

Anticonvulsants

Post-traumatic seizures (PTS) are classified as early, occurring within 7 days of injury, or late, occurring 7 days after the injury (48). The incidence of PTS in head injury victims from various studies varies between 4 and 25%; the incidence of late PTS varies between 9 and 42% (48). Phenytoin may be used to prevent early PTS in patients at high risk for seizures after head injury, and in one study, decreased the incidence from 14.2 to 3.6% (48). Other studies have not found prophylactic phenytoin to be beneficial in preventing early PTS (49).

It was once thought that the prevention of early seizures would prevent the development of late PTS or epilepsy (30, 48). However, prophylactic use of antiepileptic drugs has not been demonstrated to be effective in preventing late PTS (50). Consequently, because of their unproven benefit and the numerous potential side effects, routine use of anticonvulsants after the first week of severe head injury is not recommended.

Steroids and Hypothermia

Most available evidence suggests that corticosteroids do not lower ICP or improve outcome in patients with severe head injuries (6, 51–53). Mild and moderate hypothermia (32–33°C) has improved neurologic outcomes in certain models of experimental brain injury (28) and has shown good recovery in 8 of 10 patients with a GCS <4 (55). Further studies are necessary to clarify the role of hypothermia in patients with severe head injuries.

Oxygen-Derived Free Radical Scavengers

The role of oxygen-derived free radical scavengers in preventing secondary brain injury in trauma is being studied (56–58). The results of a study using polyethylene glycol-superoxide dismutase at a dose of 10,000 U/kg indicated improved outcomes when compared with placebo (56). At the present time, there are no clear recommendations for the use of oxygen-derived free radical scavengers or any number of other neuroprotective drugs that are being studied; however, it can be anticipated that in the future there will be therapies to reduce the secondary injuries caused by edema, anoxia, and acidosis.

There are other substances under consideration for use in the management of the patient with head injuries. However, thus far there are no other extensively studied substances or modalities that would be supported for use.

Conclusion

The initial evaluation and treatment of a patient with severe brain injuries entails a careful primary and secondary trauma survey with the initial focus on ensuring oxygenation and perfusion. Strict attention to the cervical spine with continual care to maintain the head in a stable midposition is imperative. Rapid sequence endotracheal intubation is recommended when airway control is required. Sedation, with or without a short-acting pharmacologic paralytic agent, may be needed in the agitated, combative patient with head injuries. Increased ICP is managed with bolus infusions of mannitol which are repeated as necessary if the patient is euvolemic and the serum osmolarity is less than 320 mOsm/L. Hyperventilation is reserved for patients who are acutely deteriorating pending mannitol therapy. An early CT scan is essential in the rapid evaluation and diagnosis. When indicated, neurosurgical definitive management of intracranial mass lesions should ensue without delay.

References

1. White RJ, Likavec MJ. The diagnosis and initial management of head injury. N Engl J Med 1992; 327:1507–1511.
2. Gabriel GM, Borel CO. Emergency treatment of patients with severe head injury. J Crit Illness 1996; 11:75–83.
3. Borel C, Hanley D, Dirninger MN, et al. Intensive management of severe head injury. Chest 1990; 98:180–189.
4. Sosin DM, Sniezek JE, Waxweiler RJ. Trends in death associated with traumatic brain injury, 1979 through 1992. JAMA 1995; 273:1778–1780.
5. Olshaker J. Head Trauma. In: Harwood-Nuss AL, Linden CH, Luten RC, Shepherd SM, Wolfson AB, editors. The Clinical Practice of Emergency Medicine. Philadelphia: Lippincott-Raven, 1996:404–408.
6. Bullock R, Chestnut R, Clifton F, et al. Guidelines for the Management of Severe Head Injury. New York: Brain Trauma Foundation, 1996.

7. Campbell JE. Basic Trauma Life Support, 3rd ed. Englewood Cliffs, NJ: Brady/Prentice-Hall, 1995:23–46.
8. Smith J Jr, Martin L, Young W, et al. Do trauma centers improve outcome over non-trauma centers: The evaluation of regional trauma care using discharge abstract data and patient management categories. J Trauma 1990; 30:1533–1538.
9. Gentleman D. Causes and effects of systemic complications among severely head injured patients transferred to a neurosurgical unit. Int Surg 1992; 77:297–302.
10. Rhee KJ, O'Malley RJ. Neuromuscular blockade-assisted oral intubation versus nasotracheal intubation in the prehospital care of injured patients. Ann Emerg Med 1994; 23:37–42.
11. Majernick TG, Bieniek R, Houston JB, et al. Cervical spine movement during orotracheal intubation. Ann Emerg Med 1986; 15:417–420.
12. Holley J, Jorden R. Airway management in patients with unstable cervical spine fractures. Ann Emerg Med 1989; 18:1237–1239.
13. Rhee KJ, Green W, Holcroft JW, et al. Oral intubation in the multiply injured patient: The risk of exacerbating spinal cord damage. Ann Emerg Med 1990; 19:511–514.
14. Chestnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma 1993; 34:216–222.
15. Vassar MJ, Fischer RP, O'Brien PE, et al. A multi-center trial for resuscitation of injured patients with 7.5% sodium chloride. The effect of added dextran 70. The Multicenter Group for the Study of Hypertonic Saline in Trauma Patients. Arch Surg 1993; 128:1003–1011.
16. Robertson CS, Goodman JC, Narayan RK, et al. The effect of glucose administration on carbohydrate metabolism after head injury. J Neurosurg 1991; 74:43–50.
17. Lam AM, Winn HR, Cullen BF, Sundling N. Hyperglycemia and neurological outcome in patients with head injury. J Neurosurg 1991; 75:545–551.
18. Young B, Oh L, Dempsey R, et al. Relationship between admission hyperglycemia and neurologic outcome of severely brain-injured patients. Ann Surg 1989; 210:466–472.
19. Sayre M, Daily S, Stein S, et al. Out-of-hospital administration of mannitol to head-injured patients does not change systolic blood pressure. Acad Emerg Med 1996; 3:840–848.
20. Miller JD, Butterworth JF, Gudeman SK, et al. Further experience in the management of severe head injury. J Neurosurg 1981; 54:289–299.
21. Walls RM. Rapid-sequence Intubation in head trauma. Ann Emerg Med 1993; 22:1008–1013.
22. Bouma GJ, Muizelaar JP. Relationship between cardiac output and cerebral blood flow in patients with intact and with impaired autoregulation. J Neurosurg 1990; 73:368–374.
23. Robertson CS, Contant CF, Gokaslan ZL, et al. Cerebral blood flow, arteriovenous oxygen difference, and outcome in head injured patients. J Neurol Neurosurg Psychiatry 1992; 55:594–603.
24. Narayan RK, Kishore PRS, Becker DP, et al. Intracranial pressure: To monitor or not to monitor. J Neurosurg 1982; 56:650–659.
25. Marmarou A, Anderson RL, Ward JD, et al. Impact of icp instability and hypotension on outcome in patients with severe head trauma. J Neurosurg 1991; 75:S159–S166.
26. Eisenberg H, Frankowski R, Contant C, et al. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. J Neurosurg 1988; 69:15–23.
27. Miller JD, Becker DP, Ward JD, et al. Significance of intracranial hypertension in severe head injury. J Neurosurg 1977; 47:503–516.
28. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. J Neurosurg 1991; 75:731–739.
29. Kerr ME. Hyperventilation and head injuries. Heart Lung 1993; 22:516–522.
30. Yablon SA. Posttraumatic seizures. Arch Phys Med Rehabil 1993; 74:983–1001.
31. Raichle ME, Plum F. Hyperventilation and cerebral blood flow. Stroke 1972; 3:566–575.
32. Marion DW, Darby J, Yonas H. Acute regional cerebral blood flow changes caused by severe head injuries. J Neurosurg 1991; 74:407–414.
33. Obrist WD, Langfitt TW, Jaggi JL, et al. Cerebral blood flow and metabolism in comatose patients with acute head injury. J Neurosurg 1984; 61:241–253.
34. Graham D, Adams JH. Ischemic brain damage in fatal head injuries. Lancet 1971; 1:265–266.
35. Wolf AL, Levi L, Marmarou A, et al. Effect of THAM upon outcome in severe head injury: A randomized prospective clinical trial. J Neurosurg 1993; 78:54–59.
36. Brown FD, Johns L, Jafar JJ, et al. Detailed monitoring of the effects of mannitol following experimental head injury. J Neurosurg 1979; 50:423–432.
37. Mendelow AD, Teasdale GM, Russel T, et al. Effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human head injury. J Neurosurg 1985; 63:43–48.
38. Rosner MJ, Coley I. Cerebral perfusion pressure: A hemodynamic mechanism of mannitol and the postmannitol hemogram. Neurosurgery 1987; 21:147–156.
39. McGraw CP, Howard G. Effect of mannitol on increased intracranial pressure. Neurosurgery 1983; 13:260–271.
40. Kassel NF, Bauman KW, Hitcon PW, et al. The effects of high dose mannitol on cerebral blood flow in dogs with normal intracranial pressure. Stroke 1982; 13:59–61.
41. Muizelaar JP, Lutz III HA, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. J Neurosurg 1984; 61:700–706.
42. Barry KG, Berman AR. Mannitol infusion, Part III. The acute effect of the intravenous infusion of mannitol on blood and plasma volume. N Engl J Med 1961; 264:1085–1088.
43. Israel RS, Marx JA, Moore EE, Lowenstein SR. Hemodynamic effect of mannitol in a canine model of concomitant increased intracranial pressure and hemorrhagic shock. Ann Emerg Med 1988; 17:560–565.
44. James HE. Methodology for the control of intracranial pressure with hypertonic mannitol. Acta Neurochir 1980; 51:161–172.
45. Marshall LF, Smith RW, Rauscher LA. Mannitol dose requirements in brain injured patients. J Neurosurg 1978; 48:169–172.
46. Kaufmann AM, Cordoso ER. Aggravation of vasogenic cerebral edema by multiple-dose mannitol. J Neurosurg 1992; 77:584–589.
47. Miller JD, Piper IR, Dearden NM. Management of intracranial hypertension in head injury: Matching treatment with cause. Acta Neurochir 1993; 57:152–159.
48. Temkin NR, Dikmen SS, Winn HR. Posttraumatic seizures. Neurosurg Clin N Am 1991; 2:425–435.

49. Young B, Rapp RP, Norton JA, et al. Failure of prophylactically administered phenytoin to prevent early post-traumatic seizures. J Neurosurg 1983; 58:231–235.
50. Young B, Rapp RP, Norton JA, et al. Failure of prophylactically administered phenytoin to prevent late post-traumatic seizures. J Neurosurg 1983; 58:236–241.
51. Gaab MR, Trost HA, Alcantara A, et al. Ultrahigh dexamethasone in acute brain injury. Zentralbl Neurochir 1994; 55:135–143.
52. Cooper PR, Moody S, Clark WK, et al. Dexamethasone and severe head injury. J Neurosurg 1979; 51:307–316.
53. Kloti J, Fanconi S, Zachmann M, et al. Dexamethasone therapy and cortisol excretion in severe pediatric head injury. Child Nerv Syst 1987; 3:103–105.
54. Clifton GL. Hypothermia and hyperbaric oxygen as treatment modalities for severe head injury. New Horiz 1995; 3:474–478.
55. Hayashi N, Hirayema T, Velagawa A, et al. Systemic management of cerebral edema based on a new concept in severe head injury patients. Acta Neurochir Suppl Wien 1994; 60:541–543.
56. Muizelaar JP. Cerebral ischemia-reperfusion injury after severe head injury and its possible treatment with polyethyleneglycol-superoxide dismutase. Ann Emerg Med 1993; 22:1014–1021.
57. Muizelaar JP, Marmarou A, Young HF, et al. Improving the outcome of severe head injury with the oxygen radical scavenger polyethylene glycol-conjugated superoxide dismutase: A phase II trial. J Neurosurg 1993; 78: 375–382.
58. Young B, Runge JW, Waxman KS, et al. Effects of pergorgotein on neurologic outcome of patients with severe head injury. JAMA 1996; 276:538–543.

Nontraumatic Intramural Hematoma of the Duodenum Complicating Warfarin Therapy

David E. Gutstein, M.D., and Stanley J. Rosenberg, M.D.

Abstract

A 74-year-old man receiving chronic anticoagulant therapy presented with symptoms of acute small bowel obstruction. He was subsequently found to have an intramural hematoma of the duodenum. Early noninvasive diagnosis was possible using computed tomography. Conservative therapy proved successful in allowing resolution of obstructive symptoms. This case illustrates the effectiveness of a conservative approach to intramural hematoma of the duodenum, even in patients requiring anticoagulation. **Key Words:** duodenum, hematoma, warfarin.

Intramural hematoma of the duodenum (IMHD) is a rare event which is usually associated with trauma. A review of 124 cases of IMHD by Jones et al. (1) showed that roughly 75% of such cases were traumatic in origin. Only 4 of these 124 cases occurred in patients who received chronic anticoagulation with warfarin (1). A review of the literature (2) has disclosed only two cases of nontraumatic, warfarin-induced IMHD since Jones et al. (1) published their study in 1971, indicating that the lesion is exceedingly rare. Several studies of the bleeding complications associated with warfarin therapy have not mentioned the occurrence of this uncommon event (3–5).

This case illustrates many of the diagnostic aspects and management issues of warfarin-associated IMHD.

Case Report

A.B. is a 74-year-old man who had a myocardial infarction in 1979 and aortic valve replacement in 1987. Since then, he has been receiving anticoagulant therapy. He was admitted to the Beth Israel Hospital on March 17, 1993, complaining of increasing abdominal bloating and the lack of stool output for 3 days, despite increased flatus and 2 days of dull aching epigastric pains without cramping. He vomited a large amount of bilious fluid at the time of admission. The patient described no trauma or melena. He had been receiving a maintenance dose of 5 mg of warfarin daily. The prothrombin time was monitored on a weekly to biweekly basis and remained consistently between 16 and 21 seconds (control of 12 seconds, INR of 2–4).

On examination, the patient was afebrile. His abdomen was markedly distended and bowel sounds were hypoactive. Neither focal nor rebound tenderness was present.

Laboratory data included a prothrombin time of 38.9 seconds (control, 10.1; INR, 14.6). Hematocrit was 33% and the white blood cell count was 8,900/mm^3. The blood chemistries were: alanine aminotransferase (ALT), 224 IU/L; aspartate aminotransferase (AST), 20 IU/L; alkaline phosphatase, 146 IU/L; total bilirubin, 0.9 mg/dL; and amylase, 135 IU/L. The abdominal x-ray was unremarkable.

Nasogastric suction was initiated and 1500 mL of bilious fluid drained during the first hospi-

---

From the Division of Gastroenterology, Department of Medicine, Beth Israel Hospital, Boston, Massachusetts. Address correspondence to David E. Gutstein, M.D., Division of Cardiology, Department of Medicine, Box 1030, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

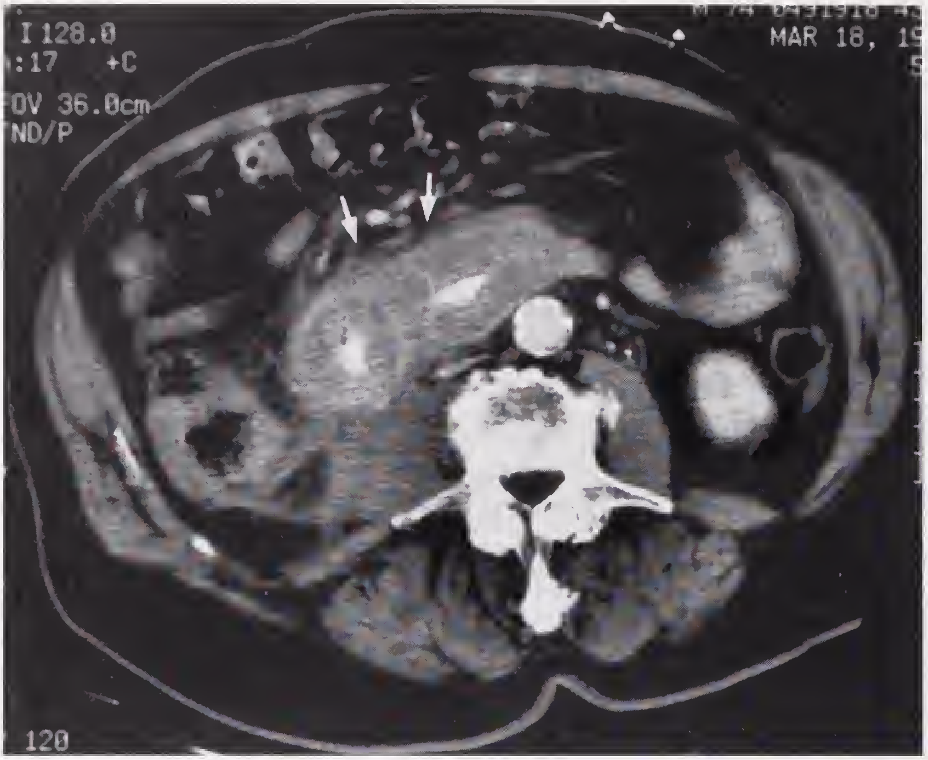


Fig. 1. Computed tomographic scan of the abdomen. A hematoma of the second and third portions of the duodenum (arrows) is illustrated. The hemorrhage extends into the right retroperitoneal space.

tal day. The patient became febrile. The white blood cell count rose to 19,700/mm^3. He was started on ampicillin, gentamicin, and metronidazole intravenously to cover a possible biliary source of infection. His total bilirubin and serum amylase peaked at 2.3 mg/dL and 215 IU/L, respectively. The hematocrit was unchanged. He was given fresh frozen plasma which corrected his prothrombin time to between 16 and 21 seconds (control, 10.1; INR, 2.5–4.2).

Abdominal ultrasound showed no evidence of gallbladder inflammation, gallstones or dilated hepatic ducts. A computed tomography (CT) scan of the abdomen revealed the duodenal and retroperitoneal hemorrhage with marked symmetrical, circumferential thickening of the duodenal wall from the second to the fourth parts of the duodenum (Fig. 1).

Approximately 2 L/day of bilious fluid were collected during the next 8 days via suction of the indwelling nasogastric tube. Total parenteral nutrition was initiated and maintained during this interval. The patient's abdominal discomfort and abnormal liver function tests rapidly resolved. During the next 2-day interval, the residual signs of upper gastrointestinal tract obstruction disappeared. The cause of the markedly elevated prothrombin time on admission was never elucidated.

Discussion

Intramural hematomas occur more frequently in the duodenum than in other areas of the bowel for a variety of reasons. It is theorized that the fixed location of the duodenum in the retroperitoneum makes this area vulnerable to even minor trauma. The highly vascular nature of the duodenum may be another factor facilitating the development of intermural hemorrhage. It has also been theorized that because the duodenum lacks a complete serosal layer, tamponade may be compromised (1, 6, 7).

Typically, IMHD presents with epigastric pain and bilious emesis (1, 6, 8, 9). Conditions predisposing individuals to IMHD, aside from trauma and warfarin toxicity, include hemophilia, pancreatitis, and alcoholism (1). Several case reports have indicated that IMHD may complicate small bowel endoscopy and biopsy (10, 11). On examination, an abdominal mass may be palpated (1). Despite some epigastric tenderness, the abdomen is usually soft. Evidence of peritoneal irritation is generally absent (8).

Laboratory abnormalities in IMHD are well described. Leukocytosis is common. The rise in serum bilirubin and amylase may be caused by obstruction of biliary and pancreatic outflow (1, 6). Plain film of the abdomen may show a dilated distorted stomach and duodenal obstruction.

The ability to diagnose IMHD has progressed with advances in imaging technology. In 1954, the "coil spring" sign appearance on barium studies of the upper gastrointestinal tract was described by Felson and Levin (12). The sign is believed to be diagnostic in the proper setting, but few patients with IMHD have this sign on prospective evaluation. However, Touloukian (8) indicated that most patients with IMHD have signs of incomplete obstruction of the duodenum without the chronic appearance described by Felson and Levin.

Ultrasound and CT scan illustrate the extent of intramural bleeding better than barium studies (13). However, no data are available comparing the sensitivity of these imaging techniques and upper GI series for diagnosing IMHD (14). Barium studies are still useful to rule out transmural leaks and to identify the point of obstruction (8, 13). A highly specific "ring sign" identifying duodenal hematoma in magnetic resonance imaging has been described (15).

In our case, CT scan was superior to ultrasound in diagnosing the presence of IMHD. Early identification clearly helped guide the subsequent course of therapy and obviate the need for further studies or exploratory surgery.

The approach to treatment of IMHD has become increasingly conservative. Reviews of the topic published in the 1960s and early 1970s suggested only a limited role for conservative therapy. Patients amenable to a nonsurgical approach were thought to include those with minimal obstructive symptoms and signs, or patients whose hematomas resulted from clotting abnormalities. The treatment of choice for IMHD in all other cases was evacuation of the duodenal hematoma, with or without gastrojejunostomy (1, 6).

The addition of total parenteral nutrition to nasogastric suction and intravenous hydration has improved the success rate of conservative management of IMHD. Both the complication rate and the length of hospital stay are now reduced in those treated conservatively compared to similar patients treated surgically (9). If patients develop peritoneal signs or their condition fails to resolve after 7 to 10 days, surgical intervention has been recommended (8, 9).

Jewett et al. (9) found that conservative treatment of IMHD in a pediatric population allowed for the resumption of oral feedings within an average of 7 days after admission. With the use of total parenteral nutrition, it is conceivable that patients may be stabilized for longer periods to allow resolution of obstruction, if necessary.

IMHD complicating warfarin therapy, without a history of antecedent trauma, is extremely rare. The diagnosis may require a combination of various noninvasive imaging studies with CT scan presently appearing to be most effective for early identification of IMHD. Conservative management, consisting of nasogastric suction, parenteral fluids and nutrition, and careful observation, appears to be more appropriate than surgical evacuation of the duodenal hematoma in uncomplicated cases.

Acknowledgments

The authors gratefully acknowledge Ms. Cynthia Meyers-Mahmood for her secretarial assistance.

References

1. Jones WR, Hardin WJ, Davis JT, Hardy JT. Intramural hematoma of the duodenum: A review of the literature and case report. Ann Surg 1971; 173:534–544.
2. Fingerhut A, Rouffet F, Eugene C, et al. Nontraumatic intramural hematoma of the duodenum: report of 4 cases and review of the literature. Digestion 1983; 26: 231–235.
3. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction and prevention. Am J Med 1993; 95:315–328.
4. Levine MN, Hirsh J, Landefeld S, Raskob G. Hemorrhagic complications of anticoagulant treatment. Chest 1992; 102(4 suppl):352S–363S.
5. Launbjerg J, Egeblad H, Heaf J, et al. Bleeding complications to oral anticoagulant therapy: multivariate analysis of 1010 treatment years in 551 outpatients. J Intern Med 1991; 229:351–355.
6. Mathewson C Jr, Morgan R. Intramural hematoma of the duodenum: a clinical entity. Am J Surg 1966; 112:299–307.
7. Wiot JF, Weinstein AS, Felson B. Duodenal hematoma induced by coumarin. Am J Roentgenol Radium Ther Nucl Med 1961; 86:70–75.
8. Touloukian R. Protocol for the nonoperative treatment of obstructing intramural duodenal hematoma during childhood. Am J Surg 1983; 145:330–334.
9. Jewett TC Jr, Caldarola V, Karp MP, et al. Intramural hematoma of the duodenum. Arch Surg 1988; 123:54–58.
10. Ghishan FK, Werner M, Vieira P, et al. Intramural duodenal hematoma: An unusual complication of endoscopic small bowel biopsy. Am J Gastroenterol 1987; 82:368–370.
11. Patel R, Shaps J. Intramural duodenal hematoma: A complication of ERCP. Gastrointest Endosc 1982; 28:218–219.
12. Felson B, Levin EJ. Intramural hematoma of the duodenum: A diagnostic roentgen sign. Radiology 1954; 63: 823–831.
13. Shirkhoda A, Mauro MA, Staab EV, Blatt PM. Soft-tissue hemorrhage in hemophiliac patients: computed tomography and ultrasound study. Radiology 1983; 147:811–814.
14. Plojoux O, Hauser H, Wettstein P. Computed tomography of intermural hematoma of the small intestine: A report of 3 cases. Radiology 1982; 144:559–561.
15. Hahn PF, Stark DD, Vici LG, Ferrucci JT. Duodenal hematoma: the ring sign in MR imaging. Radiology 1986; 159:379–382.

Splenic and Renal Infarctions Complicating Atrial Fibrillation

Athanassios Argiris, M.D.

Abstract

Splenic and renal infarctions are common manifestations of cardiac thromboembolism. Usually they remain clinically silent and are not likely to be diagnosed antemortem. Two elderly female patients, in whom nonrheumatic chronic atrial fibrillation was noted, received low-dose aspirin. Both complained of the onset of acute abdominal pain and were found to have splenic and renal infarctions on abdominal computerized tomography. An enlarged left atrium was seen on echocardiogram in both cases. Treatment consisted of hydration, analgesics, and anticoagulation. In one case, liquefactive necrosis of the splenic infarct was observed on subsequent computer tomography studies. Both patients did well and remained free of new embolic events in the following 6 and 10 months, respectively. Clinicians should readily recognize the clinical manifestations of splenic and renal infarctions in patients with atrial fibrillation. Abdominal computerized tomography can confirm the diagnosis. **Key Words:** splenic infarction, renal infarction, atrial fibrillation, systemic thromboembolism.

Systemic thromboembolism involves the viscera (including mesenteric, renal, and splenic arteries) in 9% of all cases (1). The source is usually from a thrombus in the heart (1, 2). Atrial fibrillation due to either rheumatic or nonrheumatic heart diseases increases the risk of embolic phenomena. This is presumably caused by stasis and thrombus formation in the left atrium and is present in approximately 75% of all patients with systemic thromboembolism (1). Acute occlusion of the splenic and renal arteries almost always results in infarction because they are end-arteries (2). These infarcts may be difficult to diagnose because they can be clinically silent (3–6). Consequently, there is a dearth of literature on the diagnosis and management of renal and splenic infarctions as complications of thromboembolic disease.

We discuss two patients with chronic nonrheumatic atrial fibrillation who presented with acute abdominal pain and were found to have splenic and renal infarcts on computerized tomography (CT) of the abdomen. The clinical and radiological findings and the management of the patients are discussed.

Case Reports

Case 1

An 81-year-old woman was admitted with a 1-day history of steady sharp left upper quadrant pain that radiated to the left flank. The pain worsened with body and inspiratory movements, and was associated with nausea and episodes of vomiting. She had had chronic atrial fibrillation for 15 years, and had been taking aspirin 81 mg/day for the last few years. She was not considered a candidate for warfarin by her physician because of noncompliance with follow-up visits. Her other past medical history included mild hypertension, chronic obstructive pulmonary disease, non-insulin-dependent diabetes mellitus, and lower extremity arterial disease for which she had never had a complete evaluation. She had been taking verapamil, glyburide, albuterol, and triamcinolone inhalers. She had been a heavy

---

From the Department of Medicine, Beth Israel Medical Center, New York. Address correspondence to Athanassios Argiris, M.D., 26 Barnett Street, Apt. A-22, New Haven, CT 06515.

smoker for the past 60 years. There was no family history of thromboembolic events. On review of systems she reported chronic productive cough and intermittent claudication.

She presented as an obese white woman in moderate distress secondary to pain, lying preferably on her left side to facilitate splinting. She was 160 cm tall and weighed 90 kg. Her blood pressure was 134/85 mm Hg, heart rate 118 beats/min, respiration rate 20 breaths/min and temperature 36.7°C. Cardiac examination revealed an irregularly irregular rhythm without gallops or murmurs. On abdominal examination, left upper quadrant tenderness with voluntary guarding was found. No splenomegaly could be appreciated. Results of the rectal examination were normal. The peripheral pulses were diminished. Laboratory analysis revealed a white blood cell count of 16,300/mm^3 with 89.3% polymorphonuclear leukocytes, a hemoglobin of 16.4 g/dL, and platelet count of 264,000/mm^3. Serum glucose was 333 mg/dL. The microscopic examination of the urinary sediment was unremarkable. Dipstick analysis was positive for glucose and ketones. Lactate dehydrogenase was 336 IU/mL and peaked at 384 IU/mL (normal up to 225 IU/mL) on the third day of admission. The sedimentation rate was 35 mm/hr. Serum creatinine and electrolytes, prothrombin time, transaminases, alkaline phosphatase, amylase, and creatinine kinase cardiac isoenzyme in serial measurements were within the normal range. Blood cultures were negative. The only abnormal value on analysis of the arterial blood gases was a pO_2 of 63 mm Hg. The electrocardiogram showed atrial fibrillation with a ventricular rate of 114 beats/min. The chest x-ray revealed mildly increased interstitial lung markings bilaterally consistent with chronic bronchitis, and a tortuous calcified aorta. Abdominal x-rays were normal. A CT scan of the abdomen with intravenous contrast material administration was performed. A large hypodense nonenhancing splenic lesion (Fig. 1) was seen to involve about three quarters of the spleen and extended from the splenic hilum to the periphery. Multiple small bilateral wedge-shaped hypodense nonenhancing renal lesions were also noted (Fig. 2). Both the splenic and renal lesions were better visualized after administration of intravenous contrast material. Their radiological appearances were characteristic of splenic and renal infarctions.

A transthoracic echocardiogram showed normal left ventricular size and function, but mild mitral regurgitation and an enlarged left atrium of 4.7 cm. A transesophageal echocardiogram re-

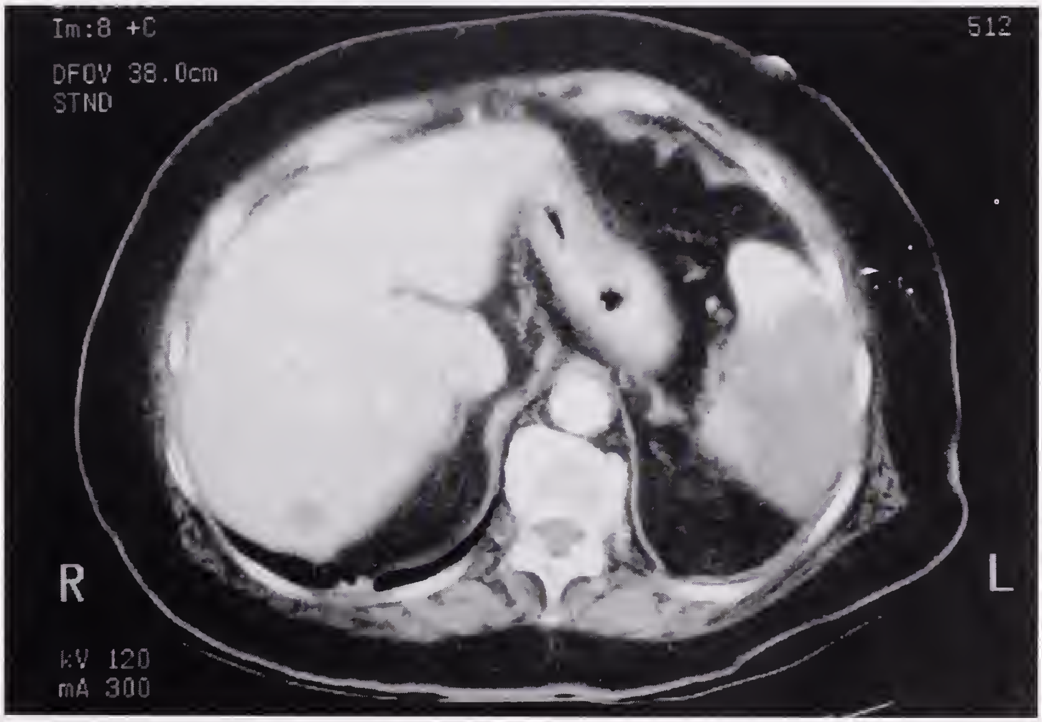


Fig. 1. Abdominal CT with IV contrast demonstrating a large wedge-shaped hypodense nonenhancing splenic lesion, occupying about three quarters of the spleen, including the splenic hilum, and extending to the periphery. The spleen measured 11 cm in length × 9.5 cm anterior-posteriorly × 5.5 cm in width (case 1).

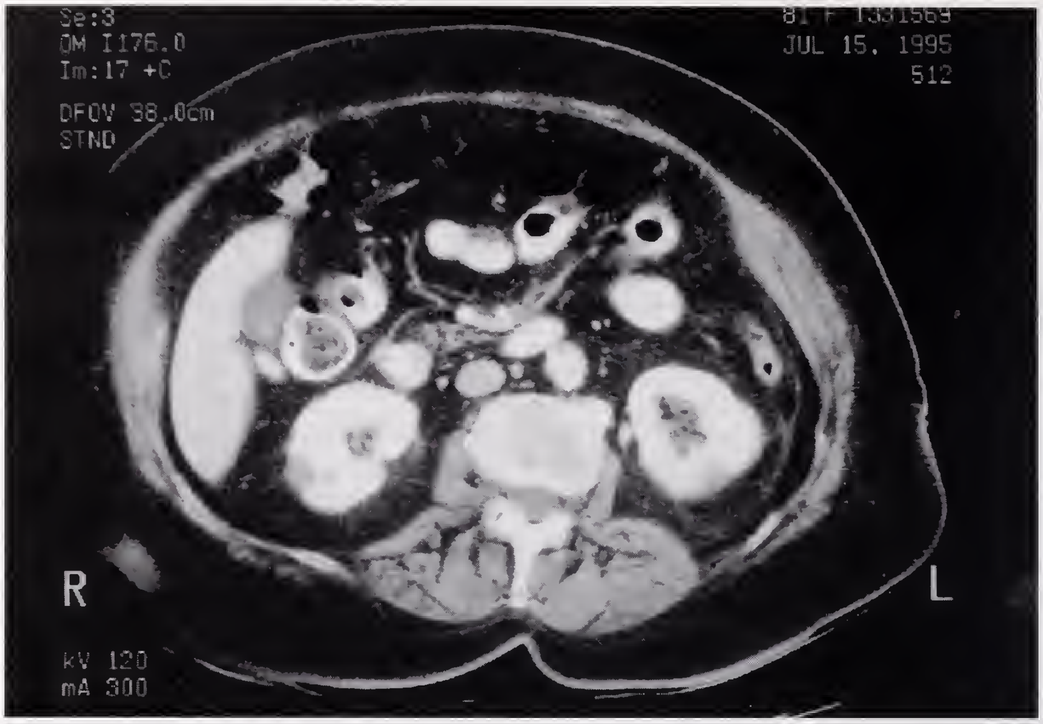


Fig. 2. Abdominal CT with IV contrast showing characteristic wedge-shaped hypodense nonenhancing defects in both kidneys. The kidney size is normal (case 1).

vealed a 2.6-cm thrombus in the left atrium and mild aortic regurgitation. No lesions were seen in the visualized part of the aorta.

Intravenous hydration, pain medication, and oxygen were administered. Serum glucose levels were controlled with subcutaneous insulin. On the third hospital day, the patient had an isolated temperature spike, up to 38.4°C, but no cause of the fever was found. Intravenous heparin was initiated on the fourth day along with warfarin. By the fifth day, the leukocytosis had subsided. However, on the fifth hospital day, the patient experienced a few episodes of acute left-sided pleuritic chest pain, and a repeat chest x-ray film showed a new left pleural effusion. A ventilation-perfusion lung scan showed matched defects to the left lower lung. A lower extremity duplex study was negative for deep venous thrombosis. The pleural effusion gradually subsided in the second week of admission. Four sonograms and three CT studies were performed during her hospitalization. The sonographic appearance of the splenic infarct was that of an irregularly marginated, echo-poor area. No kidney abnormality could be detected on sonographic evaluation. The size of the spleen was at the upper limit of normal on initial evaluation measuring 11 cm in length × 9.5 cm anterior-posteriorly × 5.5 cm in width. On the eighth day, the spleen was significantly wider, measuring 9 cm. The superior portion was round and appeared to be bulging (Fig. 3). The size and shape of the spleen remained essentially unchanged at the time of discharge. There was no evidence of hemorrhage or rupture.

The renal infarcts remained unchanged on follow-up CT studies. The patient was discharged on warfarin and did well. However, 4 weeks later, she came to the emergency room complaining of left upper quadrant abdominal pain. The physical examination and laboratory studies were unremarkable. A repeat abdominal CT showed shrinkage of the spleen to its initial size (Fig. 4). Her pain, which was thought to be nonspecific, resolved spontaneously and she was discharged the same day. She was doing well 6 months later on warfarin.

Case 2

A 66-year-old white woman complained of very recent onset of sharp right upper quadrant and right flank pain, radiating to the right thigh and accompanied by nausea and one episode of vomiting. She was in chronic atrial fibrillation. Her other past medical history included cerebral and upper and lower extremity embolism, non-insulin-dependent diabetes mellitus, hypertension, gout, right adrenalectomy for adenoma 3 years previously, and hysterectomy for fibroids. She had been hospitalized recently at another

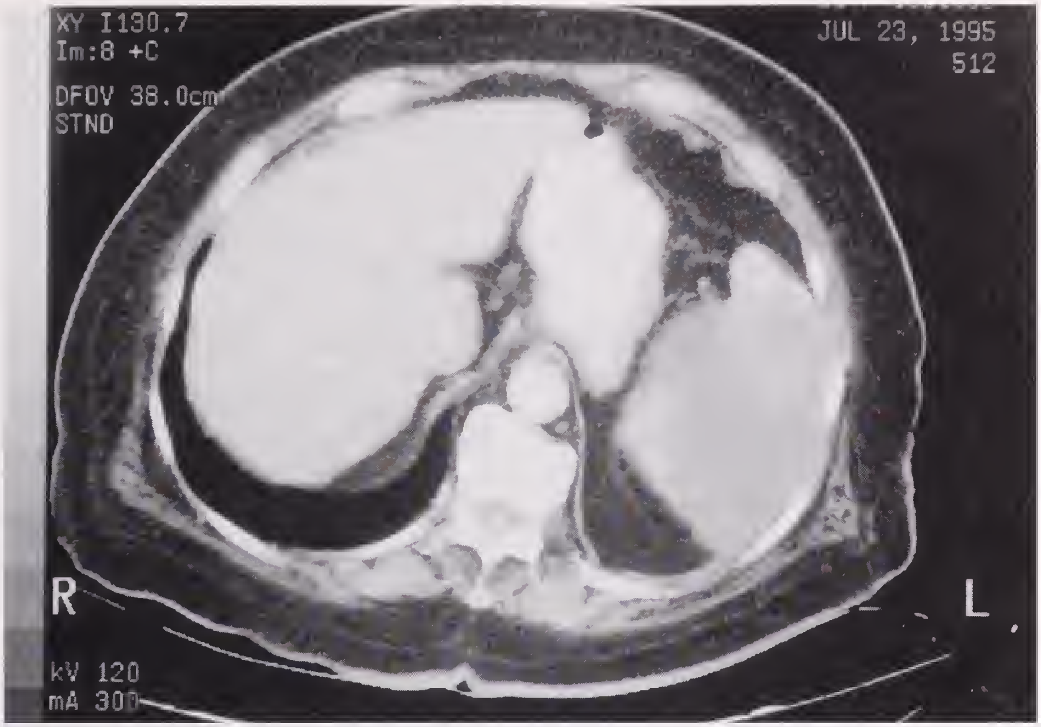

XY I130.7
Im:8 +C
DFOV 38.0cm
STND
JUL 23, 1995
512
R
L
kV 120
mA 300

Fig. 3. Follow-up abdominal CT scan performed 8 days later. The spleen is larger and bulging, with rounded configuration. It measured 9 cm in width (case 1).

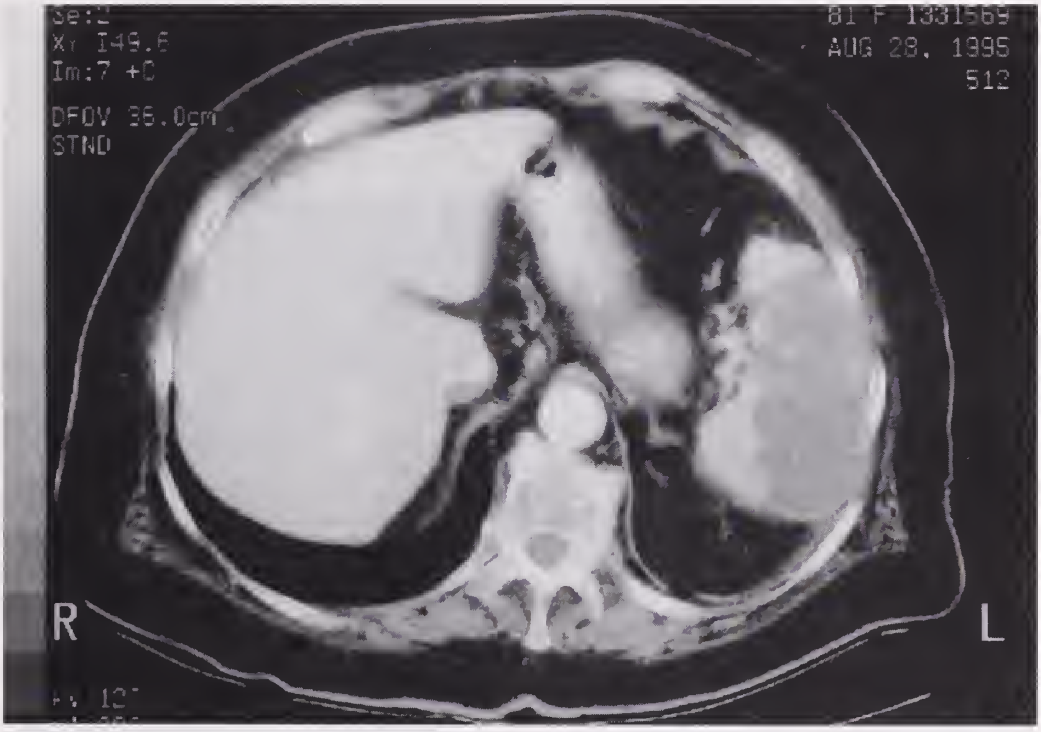

Im:7 +C
DFOV 36.0cm
STND
81 F 1331569
AUG 28, 1995
512
R
L

Fig. 4. Follow-up abdominal CT scan performed 44 days after the initial study demonstrating shrinkage and early scarring of the spleen (case 1).

hospital for an attack of gout. She was taking aspirin, 81 mg/day, verapamil, labetalol, insulin, and colchicine. The patient was reported by her primary physician to be resistant to warfarin because therapeutic levels could not be reached even with high doses of warfarin. One of her daughters experienced an episode of deep venous thrombosis at age 32.

On physical examination, the patient was 165 cm tall and obese, weighing 80 kg. She exhibited evidence of mild distress secondary to pain. She was afebrile. Her blood pressure was 148/94 mm Hg, pulse rate 100 beats/min, and respiratory rate 20 breaths/min. The neurological examination revealed residual sensory and motor deficits on the left side of the face, left arm and hand. The cardiac examination detected an irregularly irregular rhythm and rate, but without gallops or murmurs. On abdominal examination, she had right upper quadrant tenderness with voluntary guarding, as well as right costovertebral angle tenderness, without rebound tenderness or organomegaly. A complete blood count and analyses of the serum for sodium, potassium, chloride, bicarbonate, creatinine, amylase, uric acid, and creatinine kinase cardiac isoenzyme were normal. Urea nitrogen and glucose were elevated to 35 mg/dL and 219 mg/dL, respectively. Lactate dehydrogenase was 438 IU/mL and peaked at 722 IU/mL (normal up to 225 IU/mL) on the second day of admission. Transaminases were mildly elevated with aspartate aminotransferase (AST) 45 U/L and alanine aminotransferase (ALT) 97 U/L. Alkaline phosphatase was 201 U/L (normal up to 125 U/L). The microscopic examination of the urinary sediment showed 10 white and 2 red cells per high-power field. Dipstick analysis was positive for protein. Urine culture and blood cultures were negative. A work-up for hypercoagulable state was negative.

The electrocardiogram showed atrial fibrillation and a ventricular rate of 94 beats/min. The chest x-ray revealed mild cardiomegaly, a tortuous calcified aorta, and degenerative joint disease of the spine. Abdominal x-rays were negative. A CT scan of the abdomen with intravenous contrast material administration was performed the next day. A peripheral hypodense nonenhancing wedge-shaped lesion was seen within the spleen (Fig. 5), whereas the right kidney demonstrated one large, and at least two smaller, low-density nonenhancing wedge-shaped lesions occupying its upper and middle portions (Fig. 6). The spleen was normal in size, measuring 10.8 cm in length × 9.1 cm anterior-posteriorly × 5.4 cm in width. These findings were characteristic of splenic and renal infarctions and were new when compared with an abdominal CT scan performed 1 year before. A transthoracic echocardiogram showed mild mitral, aortic, and tricuspid regurgitation, an enlarged left atrium of 6.1 cm, and minimal pulmonary hypertension, while left ventricular size and function were normal. A transesophageal echocardiogram showed similar findings and was negative for left atrial thrombus. The ascending aorta was free of thrombi or atherosclerotic debris. The patient was treated with analgesics and hydration. On the second day she started to receive heparin intravenously. She became asymptomatic on the sixth day of admission. A repeat

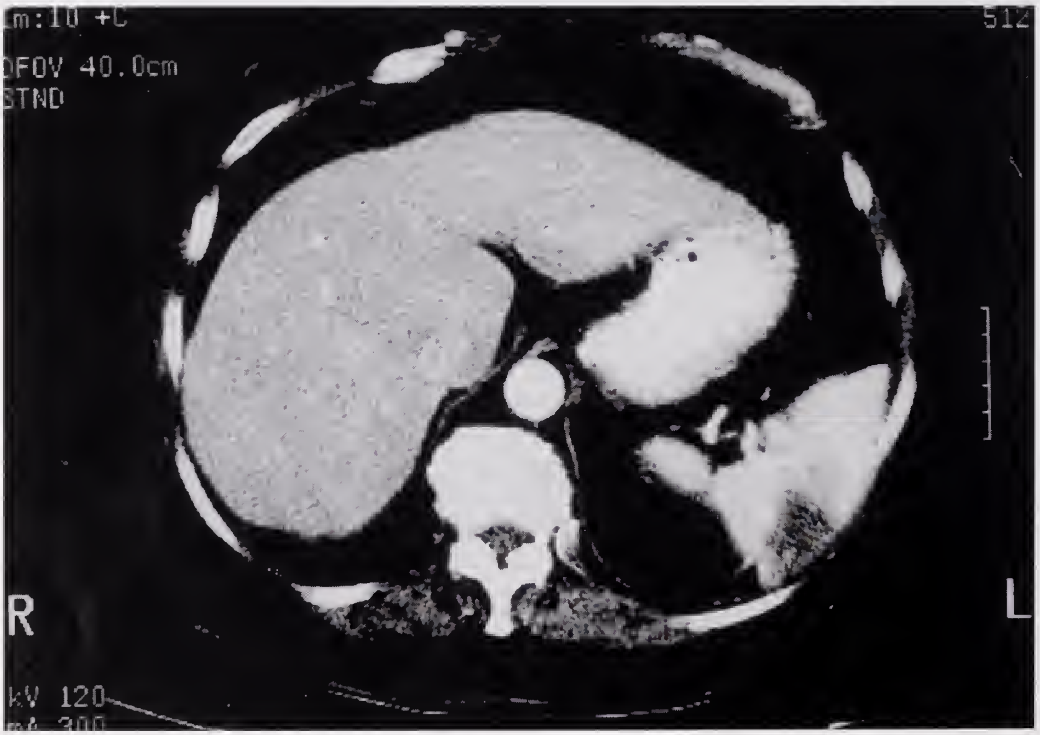


Fig. 5. Abdominal CT with IV contrast demonstrating a peripheral low-density nonenhancing wedge-shaped splenic lesion. The spleen was normal in size (case 2).

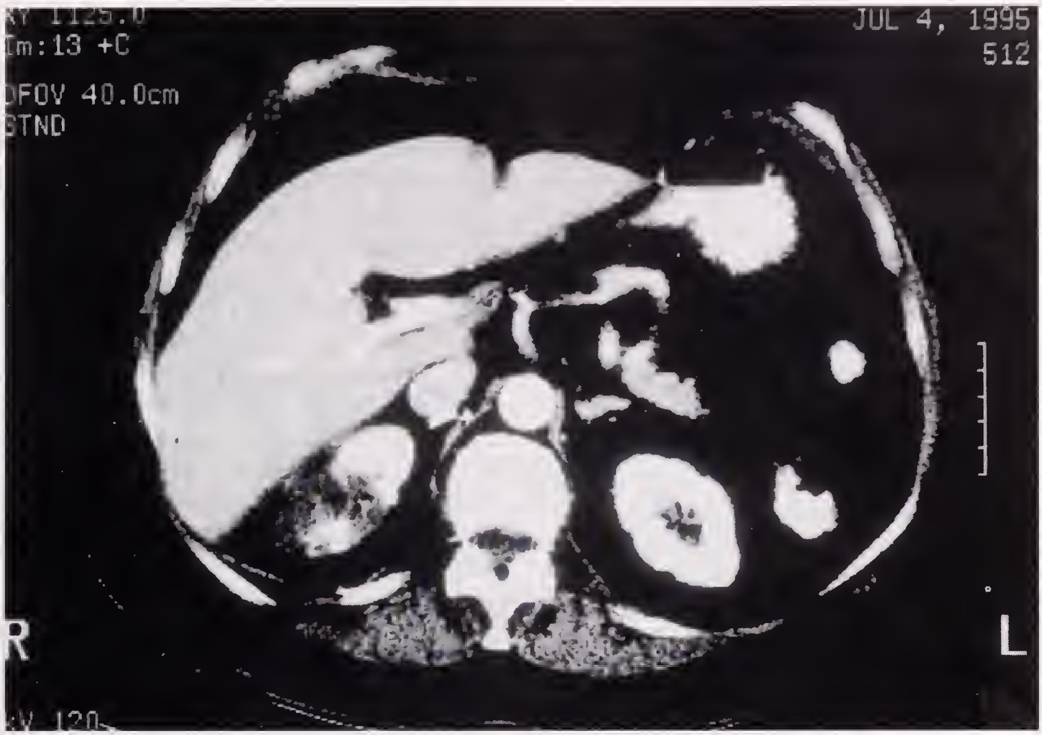


Fig. 6. The right kidney demonstrated one large, and at least two smaller low-density nonenhancing wedge-shaped lesions, occupying its upper and middle portions (case 2).

CT was done on the eighth day and showed no significant changes in the splenic and renal infarctions. The patient was discharged on subcutaneous heparin.

Two months later, she was readmitted to this hospital for near-syncope attributed to bradyarrhythmia. A magnetic resonance imaging of the abdomen disclosed scarring and shrinkage of the right kidney. The splenic infarct was well visualized and unchanged. She developed polyuria (4–6 L/day) with urine osmolality of 89 mOsm/kg. Creatinine clearance was normal. She was treated with desmopressin and a thiazide diuretic. A specific diagnosis of diabetes insipidus was never proven. Her polyuria gradually resolved. A ventricular demand inhibited (VVI) pacemaker was inserted for symptomatic bradycardia. She had no further embolic events and was doing well 8 months later with subcutaneous self-injections of heparin.

Discussion

Splenic and renal infarcts have been reported primarily in autopsy series and are often seen simultaneously (3–6). O'Keefe et al. (5) studied 96 autopsy cases of splenic infarcts of which 10% had been clinically suspected antemortem. Infarcts remote from the spleen were described in 60 of those cases, involving the kidneys in most cases (62%). Hoxie and Coggin (6) identified 205 autopsy cases of renal infarcts, of which only 1% had been diagnosed antemortem, with infarcts of other organs being present in 69% of the cases. The spleen was involved in 91 cases. Renal infarctions were commonly multiple and bilateral.

The antemortem simultaneous diagnosis of splenic and renal infarctions has rarely been reported. Haft et al. (7) reported 25 consecutive cases of bacterial endocarditis in which splenic infarction in six patients was diagnosed by abdominal CT scan. Two of these six patients had an associated renal infarction. Adler et al. (8) studied five cases of liver infarction, and reported on a patient with polycythemia vera who had liver, splenic, and renal infarcts seen on the abdominal CT scan. A symptomatic splenic and an asymptomatic right renal infarct, diagnosed by abdominal CT scan, were reported in a patient with systemic lupus erythematosus (9). Finally, incidental splenic and renal infarcts on CT were reported in a patient with embolism of the superior mesenteric artery (10).

Splenic and renal infarctions may occur in a variety of clinical settings. The most common is thromboembolism as a complication of cardiac diseases such as atrial fibrillation, myocardial infarction, rheumatic heart disease, and endocarditis. However, a significant number of splenic infarctions can be associated with hematologic diseases, especially in younger patients (3). Associated symptoms may include nausea and vomiting, and occasionally fever (3, 5, 11). Leukocytosis and elevation of lactate dehydrogenase are common in splenic and renal infarction (3, 5, 11). Pyuria and proteinuria, as noted in case 2, can be seen with renal infarcts (11).

The appearance of a wedge-shaped, nonenhancing lesion on abdominal CT with IV contrast is usually diagnostic of an infarct (14). In our first patient we described an enlarging-bulging hypodense splenic lesion that most likely represented a splenic infarct undergoing liquefaction. This lesion eventually diminished in size. Liquefactive necrosis of a splenic infarct has previously been described in the clinical setting of polycythemia vera, chronic myelogenous leukemia, and Whipple's disease (13, 14). Frequent clinical and radiological monitoring is critical in the management of patients with acute splenic infarction, and can disclose signs of serious complications such as hemorrhage, rupture, abscess, and pseudocyst, which can occur in 20% of all patients and may necessitate splenectomy (3, 14).

Arteriography is considered to be the gold standard for the radiological diagnosis of renal artery occlusion and infarction (11). However, abdominal CT scan with contrast, which is less invasive, appears to be as reliable in diagnosing renal infarction. Ultrasound could not detect the renal infarcts in one of the cases reported, but it may be cost effective for follow-up studies. Renal failure may complicate unilateral renal embolism (11). Our patients maintained normal renal function. The suspected temporary occurrence of possible nephrogenic diabetes insipidus in case 2 is unexplained. Atrophy and scarring of the infarcted kidney was demonstrated on subsequent imaging in case 2.

Transesophageal echocardiography is invaluable in locating the possible origin of emboli, especially when a left atrial thrombus, a patent foramen ovale, and/or ulcerated aortic plaques and thrombi are detected (15). Atrial fibrillation was the most likely cause of thromboembolism in our patients.

Anticoagulation therapy, as well as thrombolysis, have been used in the management of acute renal artery occlusion (11). The role of anticoagulation in the management of acute splenic artery occlusion has not been investigated. Our patients received heparin intravenously (which was started more than 24 hours after presentation) without developing hemorrhagic complications. Their subsequent management included long-term anticoagulation which was not a part of their previous treatment.

There is a growing literature on the use of anticoagulation for the prevention of thromboembolic events, mainly strokes, in patients with nonrheumatic atrial fibrillation (16–20). Risk factors for thromboembolic events in nonrheumatic atrial fibrillation include hypertension, diabetes, history of a previous thromboembolic event, and global left ventricular dysfunction or enlarged left atrium on echocardiogram (16, 17). It is very possible that anticoagulation protects against the occurrence of visceral thromboembolism as well. However, the total number of events of noncerebral thromboembolic events in SPAF (Stroke Prevention in Atrial Fibrillation) I and II as well as in the Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation (Danish AFASK) study is too small to permit definitive evaluation (18–20). Low-dose aspirin failed to protect against the occurrence of visceral thromboembolism.

References

1. Abbot WM, Maloney RD, McCabe CC, et al. Arterial embolism: A 44 year prospective. Am J Surg 1982; 143: 460–464.
2. Cotran RS, Kumar V, Robbins SL, et al. Pathologic Basis of Disease. 5th ed. Philadelphia: WB Saunders; 1994. p. 110–112.
3. Jaroch MT, Broughan TA, Hermann RE. The natural history of splenic infarct. Surgery 1986; 100:743–749.
4. Quinones-Baldrich WJ. Acute arterial and graft occlusion. In: Moore WS, editor. Vascular Surgery. A Comprehensive Review. 4th ed. Philadelphia: WB Saunders; 1993. p. 648–672.
5. O'Keefe JH Jr, Holmes DR, Schaff HV, et al. Thromboembolic splenic infarction. Mayo Clin Proc 1986; 61:967–972.
6. Hoxie HJ, Coggin CB. Renal infarction. Statistical study of 205 cases and detailed report of unusual case. Arch Intern Med 1940; 65:587–594.
7. Haft JI, Altieri J, Smith LG, Herskowitz M. Computer tomography of the abdomen in the diagnosis of splenic emboli. Arch Intern Med 1988; 148:193–197.
8. Adler DD, Glazer GM, Silver TM. Computer tomography of liver infarction. Am J Roentgenol 1984; 142:315–318.
9. Arnold MH, Schrieber L. Splenic and renal infarction in systemic lupus erythematosus: Association with anticardiolipin antibodies. Clin Rheumatol 1988; 7:406–410.
10. Feldberg MA, Mali WP. Computer tomographic diagnosis of superior mesenteric artery embolic thrombosis associated with renal and splenic infarction. Cardiovasc Intervent Radiol 1984; 7:306–308.
11. Lessman RK, Johnson SF, Coburn JW, Kaufman JJ. Renal artery embolism. Clinical features and long term follow up of 17 cases. Ann Intern Med 1978; 89:477–482.
12. Balcar I, Seltzer SE, Davis S, Geller S. CT patterns of splenic infarction: A clinical and experimental study. Radiology 1984; 151:723–729.

13. Downer WR, Peterson MS. Massive splenic infarction and liquefactive necrosis complicating polycythemia vera. Am J Roentgenol 1993; 161:79–80.
14. Goerg C, Schwerk WB. Splenic infarction: Sonographic patterns, diagnosis, follow up, and complications. Radiology 1990; 174:803–807.
15. Belkin RN, Chaundhry S, Chung J, et al. Detection of ascending aorta thrombi with transesophageal echocardiography in patients with systemic embolization. Am Heart J 1995; 130:1294–1295.
16. The Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. Ann Intern Med 1992; 116:6–12.
17. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994; 154:1449–1457.
18. Stroke Prevention in Atrial Fibrillation Investigators. Stroke prevention in atrial fibrillation study. Final results. Circulation 1991; 84:527–539.
19. Petersen P, Boyesen G, Godtfredsen J, et al. Placebo-controlled randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet 1989; 1:175–179.
20. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II study. Lancet 1994; 343:687–691.

The Stuck Catheter:

A Case Report

Philip K. Ng, M.D.,[1] Mark J. Ault, M.D.,[1] and Michael C. Fishbein, M.D.[2]

Abstract

Complications after the use of central venous catheters have become more frequent as their use in therapy has increased. As a result, the recognition and management of central venous catheters must be emphasized. We describe a unique problem, that of the "stuck catheter," and its safe and simple solution. **Key Words:** central venous catheterization, peripheral catheterization, peripherally inserted central catheter (PICC), fibrin sheath, fibrous sheath.

Central venous catheterization has become routine. In particular, the use of peripherally inserted central catheters (PICCs) has grown dramatically in recent years. Although complications of central venous catheterization have been well described, most have focused on the risk encountered during insertion (cardiovascular complications and bleeding) and during maintenance (infection and mechanical problems). We describe the unusual occurrence of a "stuck catheter," a catheter which could not be readily removed. The pathophysiology is discussed, and a simple bedside procedure for removal is described.

Case 1

A 31-year-old woman with primary pulmonary hypertension required a PICC for prostacycline infusion. A 50-cm-long, single-lumen, 3 French silicone catheter was inserted into the left basilic vein. There were no problems with the PICC until 421 days after insertion when it developed a leak. Initial attempts at removing the catheter were met with significant resistance. A chest x-ray showed that the PICC was in good position, without knotting or entanglement. Calcifications adjacent to the catheter were not seen. Various maneuvers were performed, including gentle constant traction, warm compresses, and arm repositioning. The patient experienced a tearing pain in the left upper arm as the catheter was withdrawn approximately 10 cm. Further attempts at removal were unsuccessful. At this point, lidocaine 1% was injected subcutaneously to achieve local anesthesia at a site 2–3 cm proximal to the insertion site overlying the path of the vein. A 1-cm transverse incision was made (Fig. 1). The vein was identified and incised longitudinally. This facilitated easy removal of the proximal and distal ends of the catheter along with an adherent, intact sheath. Gross inspection of the catheter indicated that the adherent material was located approximately 20 cm from the distal end correlating with the location of the "tearing pain" (Fig. 2). Pathologic examination revealed dense calcified fibrous connective tissue without an adherent inflammatory response (Fig. 3).

Case 2

A 39-year-old woman with breast cancer required a PICC for chemotherapy infusion. A 50-cm-long, 4 French, single-lumen hydromer-coated polyurethane catheter was inserted into the right basilic vein. There were no problems with the PICC. On completion of her course of therapy

---

From the [1]Division of General Internal Medicine and the [2]Department of Pathology & Laboratory Medicine, CSMC Research Institute, Cedars-Sinai Medical Center, Los Angeles, California. Address correspondence to Mark J. Ault, M.D., CSMC Research Institute, Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Room B-113, Los Angeles, CA 90048.

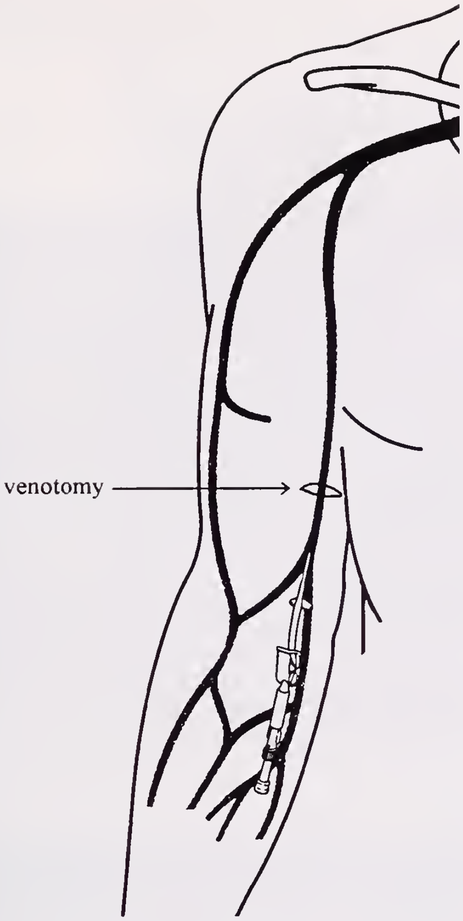


Fig. 1. Illustration demonstrating a catheter and the location of the venotomy. Reproduced with permission from Cook® Critical Care.

some 85 days after insertion, the catheter was scheduled to be removed. Initial attempts at removing it met with considerable resistance. A chest x-ray showed that the PICC was in good position. A proximal venotomy as described in Case 1 was performed, and on removal, a surrounding adherent, intact sheath was noted.

Discussion

It has been well demonstrated that the body reacts to implanted devices by coating them with a proteinaceous film containing various proteins such as fibrin, fibronectin, collagen, and immunoglobulins. This fibrin sheath can form around an intravenous catheter within 24 hours (1, 2) and may occlude the infusion holes and impair the usefulness of the catheter. However, if the sheath is associated with thrombus formation, which causes the catheter to adhere to the vessel intima without blocking the infusion holes, fluid flow through the catheter remains unimpaired. In this situation, ultimate removal of the catheter may be difficult.

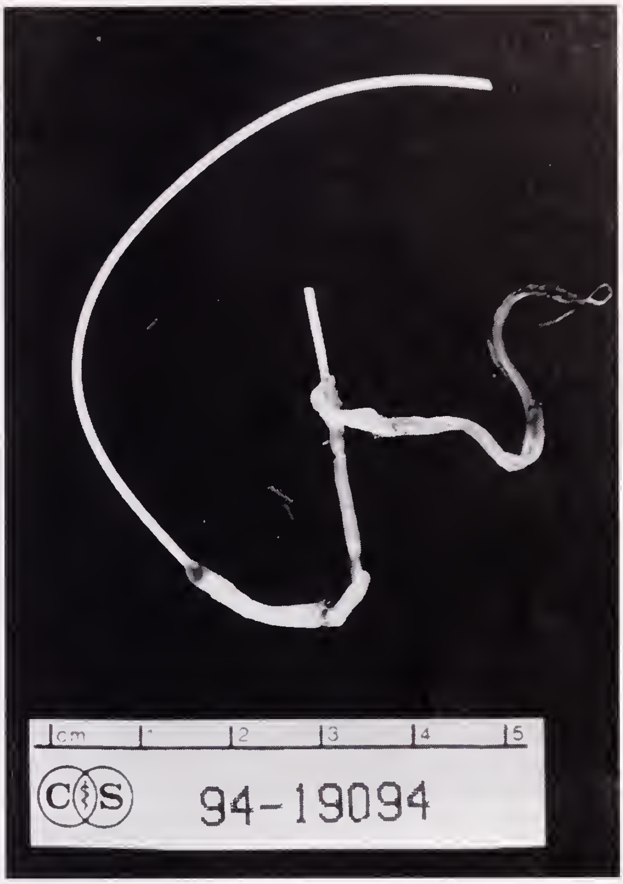


Fig. 2. Photograph illustrating the catheter encased in the fibrous sheath.

To eliminate sheath formation, Borrow and Crowley (3) have made three important recommendations: 1) the catheter should be pliable; 2) the catheter should not be in contact with the intima; and 3) preferably, a truly nonthrombogenic catheter material should be developed. The least thrombogenic catheters are those made of polyurethane coated with hydromer and silicon. Polyurethane catheters without hydromer were the most thrombogenic (3). Attempts have been made to inhibit fibrin sheath formation by using material in which heparin has been bonded, but this has not been proven to be beneficial (1, 3).

Reports of "stuck catheters" are unusual. Cardella et al. (4) described a case in which a PICC developed catheter occlusion 360 days after insertion. Removal of the catheter was complicated by a fibrin sheath which adhered to both vein intima and catheter. This catheter was removed by using a gooseneck snare inserted through a branch vein feeding into the vein which housed the PICC. The gooseneck snare described by Cardella et al. (4) may not be readily available in some centers. In addition, the presence of a branch vein feeding into the involved vessel is quite fortuitous and requires significant operator

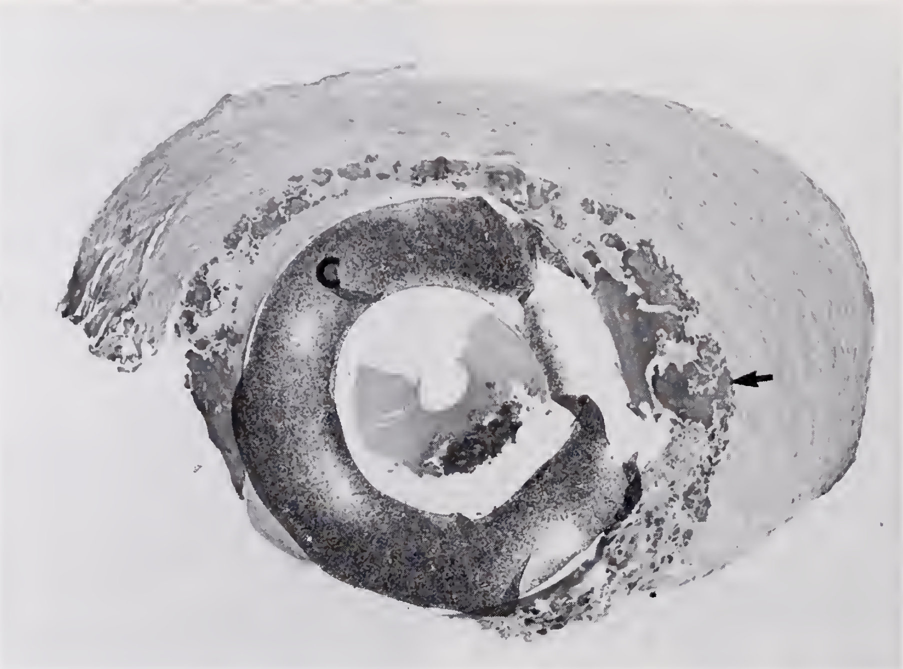


Fig. 3. Cross-section of catheter (c) surrounded by heavily calcified (arrow) dense fibrous tissue (hematoxylin and eosin stain, magnification ×10).

skill. Morimoto et al. (5) described two cases of stuck catheters. In one case, surgery was required to remove a 5-cm portion of the catheter, which broke as a result of excessive traction and remained in the patient. The other catheter was removed after systemic infusion of urokinase for thrombolysis. However, the use of intravenous thrombolytics is associated with enhanced risk of bleeding which may be exaggerated if a surgical procedure is required. Furthermore, this therapeutic approach requires hospitalization, which adds significantly to the cost of removing the catheter.

The removal of the catheter through the original puncture site in both of our patients was prevented by an adherent fibrous sheath. Proximal venotomy allowed for easy withdrawal of the catheter without breakage and without embolization of the remnant fibrous sheath. Although we are not aware of vein avulsion and significant bleeding related to catheter removal, the pain experienced by our first patient suggests the potential for this occurrence.

Prevention of the problem is clearly important. Cardella et al. (4) recommended routine catheter exchange at 270 days. However, Merrell et al. (6) and Legha et al. (7) have described PICCs dwelling for 370 and 521 days, respectively, without complications. Our cases demonstrate that a catheter can become adherent during either "long-term" or "short-term" use. Because prophylactic catheter removal is associated with possible loss of venous access and the additional risks of reinsertion, we do not recommend prophylactic catheter exchange. The effectiveness of anticoagulation, such as low-dose warfarin, to prevent fibrin deposition is unclear.

In conclusion, we have described a unique complication of PICC, the "stuck catheter," and a method of catheter removal which is safe and simple.

References

1. Lloyd DA, Shanbhogue LKR, Doherty PJ, et al. Does the fibrin coat around a central venous catheter influence catheter-related sepsis? J Pediatr Surg 1993; 28:345–349.
2. Warren PR, Bush WH, McIntyre RD, Hill LD. The development of fibrin sheath on indwelling venous catheters. Surg Gynecol Obstet 1973; 137:43–47.
3. Borrow M, Crowley G. Prevention of thrombosis of central venous catheters. J Cardiovasc Surg 1986; 27:571–574.
4. Cardella JF, Lukens ML, Fox PS. Fibrin sheath entrapment of peripherally inserted central catheters. J Vasc Interv Radiol 1994; 5:439–442.
5. Morimoto T, Hosoya R, Matsufuji H, et al. Difficulty in removing a percutaneous central venous catheter inserted from a peripheral vein. Acta Paediatr Jpn 1993; 35:352–353.
6. Merrel SW, Peatross BG, Grossman MD, et al. Peripherally inserted central catheters—low risk alternatives for ongoing venous access. West J Med 1994; 160:25–30.
7. Legha S, Haq M, Rabinowits M, et al. Evaluation of silicone elastomer catheters for long-term intravenous chemotherapy. Arch Intern Med 1985; 145:1208–1211.

Dermatology Notes

Acute Meningococcemia

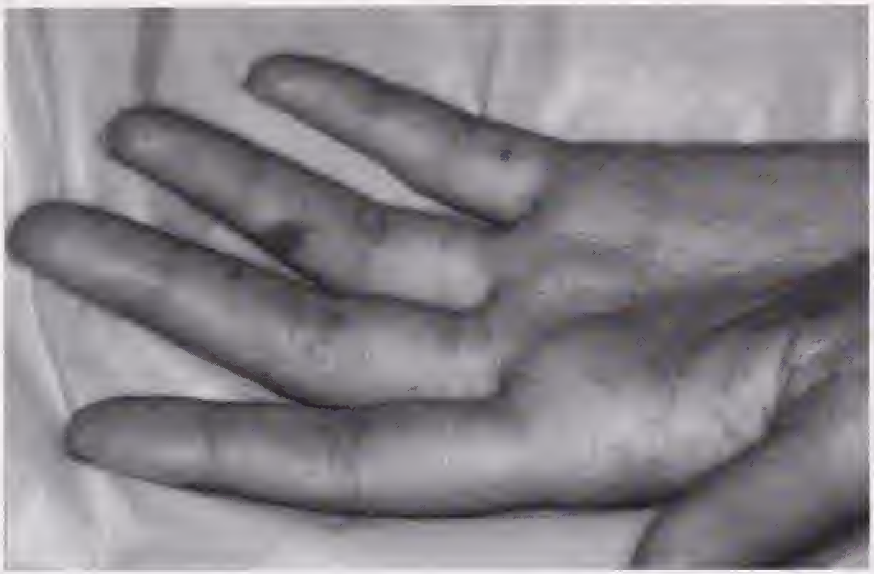


Fig. 1. Left hand: several petechiae and one purpuric macule are seen.

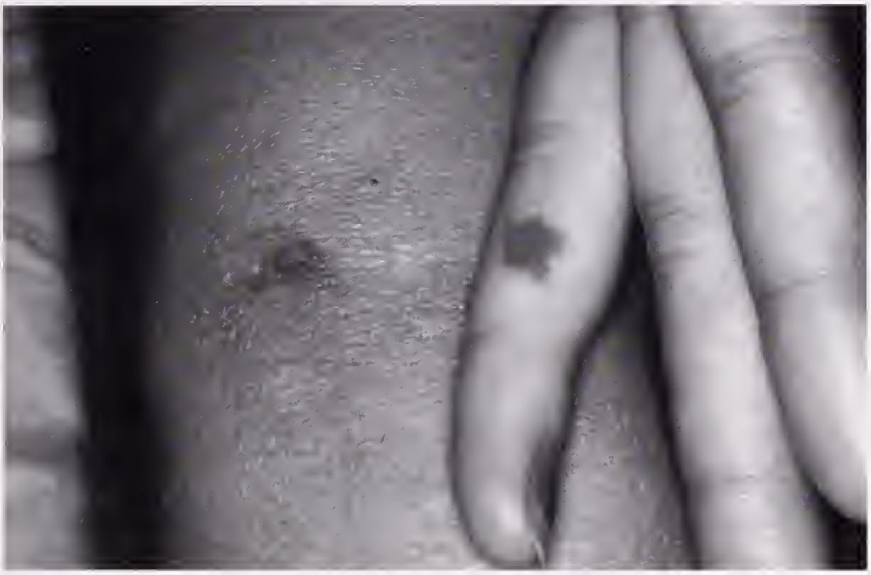
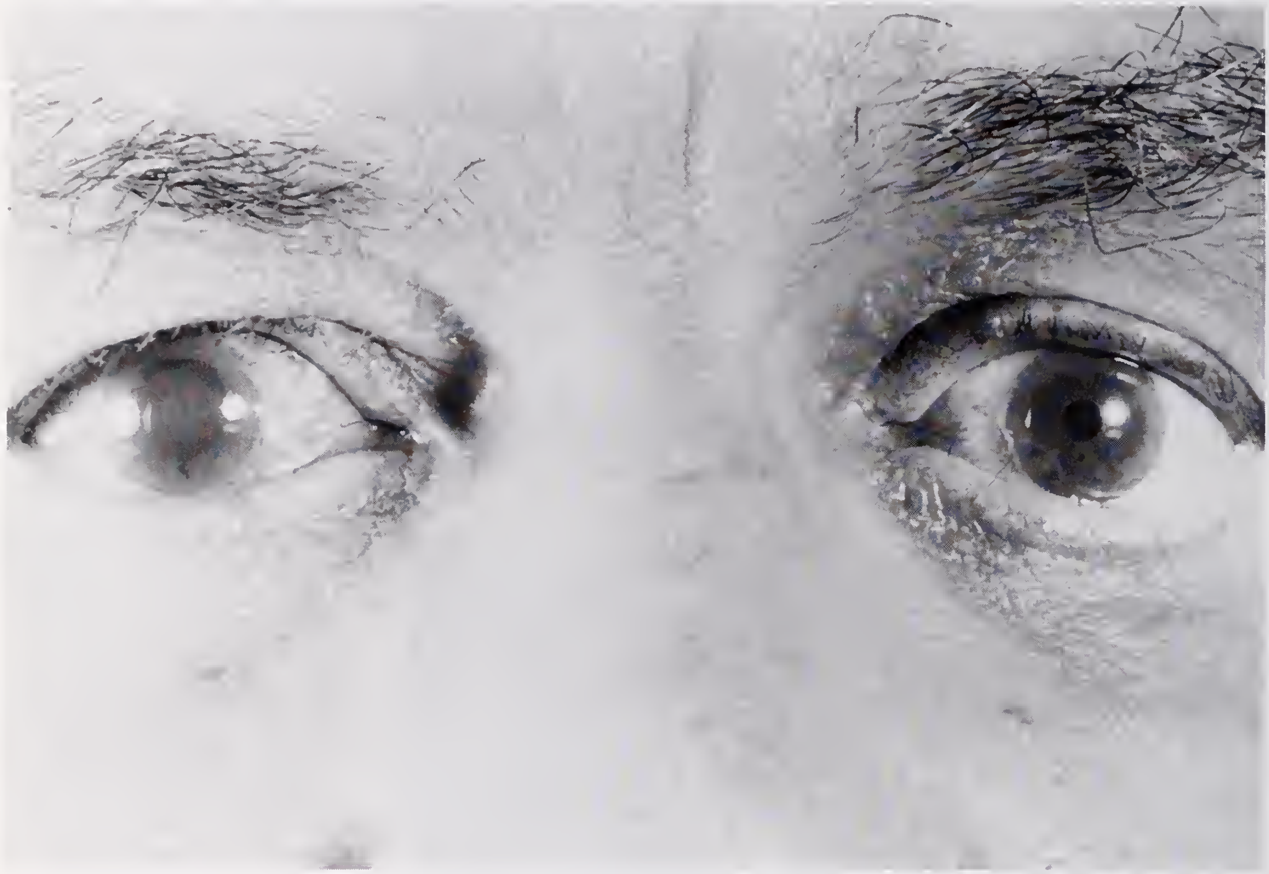


Fig. 2. Right knee and left hand: purpuric macule with vesiculated center is seen on the knee and is juxtaposed to the same purpuric macule shown in Fig. 1.

A 20-year-old Hispanic woman presented with fever, chills, severe headache, photophobia, stiff neck, and abdominal pain. Examination also revealed several petechiae and purpuric macules on the palms and digits (Fig. 1) and the right knee. The same macule on the left hand in Fig. 1 is shown again, juxtaposed to a purpuric macule on the right knee (Fig. 2). The latter lesion had a pale, grayish vesiculated center, which is a characteristic finding in acute meningococcemia. A punch biopsy of the lesion on the right knee was performed, and a Gram stain of a touch preparation was examined. Gram-negative diplococci were identified. *Neisseria meningitidis* was subsequently cultured. Extensive maplike areas of cutaneous infarction may be seen as a result of disseminated intravascular coagulation.—*Allen Sapadin, M.D., Marsha Gordon, M.D., and Edward J. Bottone, Ph.D.*

Angle-Closure Glaucoma



A 60-year-old Hispanic man with medical history of alcohol abuse presented at the emergency room with a 24-hour history of increasing pain and blurring of the right eye. Physical examination was remarkable for the right eye, which showed conjunctival injection, corneal haze, and a fixed, mid-dilated pupil, classic signs of acute angle-closure glaucoma. Visual acuity was 20/400 OD and 20/30 OS. Intraocular pressure was 60 OD and 16 OS (normal range, 10–21 mm Hg). A prompt laser iridotomy OD brought immediate pain relief and reduced the intraocular pressure to 20.—*Arif Khan, M.D.*

BOOK REVIEWS

Our Health, Our Lives: A Revolutionary Approach to Total Health Care for Women

Ellen S. Hoffman, M.D. New York: Pocket Books, a division of Simon & Schuster Inc.; 1995. 428 pp, $24.00. ISBN 0-671-88085-3.

In this 428 page book, Dr. Hoffman demonstrates how medicine can function when it serves women's needs and its shows women how to help start that process in their own lives. She advocates an unprecedented, total health care system specifically designed for women.

In this ambitious undertaking, the author has divided her subject into four parts: The Woman-Centered Approach, Total Health in Context, Women's Life Cycles, and Mind and Body Together. She draws heavily on her personal experience as she deals with each of these subjects which makes it easy for lay readers to relate to the subject matter. The personal anecdotes are heavily biased toward her experience with patients who have been mistreated, misdiagnosed, mismanaged, and misunderstood by the male medical community. The theme of the book is relevant and the author is responding to the needs of women who have been touched by the consciousness-raising that has resulted from the women's "awareness" movement. She has attempted to provide a rung in the ladder of consciousness-raising as it applies to health care, hoping to assist women in their climb toward equality in all aspects of their lives.

Even though "gender blindness" is perceived as a mechanism to facilitate the advancement and self-fulfillment of women in our society, women have also become aware that gender confers uniqueness and that in matters of health care, their needs are different. Dr. Hoffman's approach to providing "different but equal" health care to women sends a message—both implicit and explicit—that women can be cared for best by women because of a shared uniqueness resulting from gender. This is the antithesis of a dictum, which is central to the concept of the medical profession, that good medicine cannot be practiced without empathy. The basic medical school curriculum attempts to impart data and an approach to using the data to literally "care for" people of all ages, genders, ethnic and economic backgrounds as they present with diseases that are either global or specific to these various populations. Specialization in the care of any one group of patients or one organ system does not release the physician from the mandate of "caring for" all patients. The central assumption of medical training is that you don't have to have experienced the disease to provide the best care to the patient who has the disease. Why make the assumption that the experience of womanhood is necessary to provide the best care for women?

That at certain times and in certain ways members of the medical profession have defaulted in approaching their patients with sufficient empathy is incontrovertible, as is the fact that the medical profession has a long history of male predominance. The paternalism that this has engendered has resulted in many sins of commission and omission in women's health care. However, the approach of "separate but equal" care for women by women is neither a feasible nor an ethical solution to past mistakes. The solution must be bipronged. The women's awareness movement, along with affirmative action, has already resulted in the training of more women physicians. However, only a fraction elect to practice primary care. Thus, the infusion of women available to take care of women will not satisfy the demands, especially with the female predominance in the population and the tendency of women to seek care with greater frequency than men.

The other solution is to engage in male consciousness-raising about the needs of Women's Health Care. This would be a far more effective way of using the available personnel. The emphasis on and requirements for continuing medical education provides an excellent vehicle for educating the existing male medical community in matters of Women's Health. Recognition of this previously neglected "subspecialty" of medicine should lead to the development of educational material that would reorient practicing male physicians toward providing the unique care that the female population requires. Education of the "mature" male physician coupled with changes in the basic medical school curriculum to emphasize this need and optimize the particular education required should result in a marked improvement in health care delivery in women.

Dr. Hoffman's book is for lay people. They are unlikely to be aware of the number of medically incorrect statements it contains. However, because Dr. Hoffman has taken care to avoid encouraging self-care and repeatedly emphasized the need for the patient to discuss her medical problems with her physician, these inaccuracies and misconceptions are likely to be corrected by the patient's physician. The correctness and currency of the medical information presented are of less concern than the possibly deleterious effect of the assertion that women physicians are preferable to male physicians. Thus, any physician recommending this book to patients should counter this assertion with the caveat that this is only one point of view and that there are legions of excellent and empathetic male physicians at their disposal who are able to respond to their unique health care needs.

Harriet S. Gilbert, M.D.
Mount Sinai School of Medicine

Keep on Running: The Science of Training and Performance

Eric Newsholme, Tony Leech, Glenda Duester. Chichester, New York, Brisbane, Toronto, Singapore: John Wiley & Sons; 1994. 443 pp, index. $17.95. ISBN 0-471-94314-2.

I was a cross-country runner in my college days and was not very good at it. However, I persisted and was rewarded by some improvement after considerable training. In fact, I would have wished to have had this text available at that time. My father was a remarkably good sprinter in his day more than 70 years ago. So I have always had an abiding interest in Track and Field events, and the true sport of sports. All three English authors of this book have backgrounds in biochemistry, and Dr. Newsholme and Ms. Duester are practitioners of the art of marathon running. Part II of the book includes a 50-page section on training schedules by Bruce Tulloh, a gold medal winner at 5000 meters in 1962. He is a biology master and coaching editor of *Runner's World.*

It is clearly true that the medical curriculum does not allow time for comprehensive understanding of the effects of exercise. Perhaps the field is no longer of any interest to society for a variety of reasons other than for the purpose of spectator entertainment. Nonetheless, with more leisure time being promised, it is conceivable that there may be a rekindling of interest in years other than when the Olympics are held.

Medical students are exposed to the anatomy, histology, and biochemical and physiologic function of skeletal and cardiac muscle, and lesser detail about smooth muscle function, but rarely is any of this information integrated into the context of human locomotion and fitness. This book then would be a winner for medical students and physicians who might have more than a passing interest in the field. I call to mind Dr. Roger Bannister who broke the barrier of the 4-minute mile. More important, this book is written in an easy and comprehensible style which would commend it to the lay person who would want to know and experience the joys and pains of running. There are interesting historical vignettes along with scientific details which are important not only to health professionals but to the athlete. These include such details as structure of muscles, the sliding filament mechanism, the brain, spinal cord and peripheral nerves, matters relating to energy and fuel, and fluid and electrolyte balance. Particular attention is paid to the female runner, the menstrual cycle, and data which, when extrapolated, seem to indicate that women will perhaps be able to run as fast as men by about the year 2035. Included in this section are some details regarding continuation of running and pregnancy. In a separate section, Section B, entitled “Advice for Women Runners,” these details include the 1985 guidelines of the American College of Obstetricians.

There is an excellent discussion of fatigue, the mind and mentality of success, diet, nutrition, and recipes. The latter do not sound as if they would be very gourmet, but perhaps a creative chef might enliven their taste without diminishing their benefit to performance.

I have reserved my final comments to the sections on training mistakes and the use of drugs. Health professionals and trainers must be thoroughly aware of these data, and surely such information would be critical to athletes. The section on injuries and advice on running shoes is a must to those engaged in the sport. The text is well referenced and provides sufficient background for those who want to get started in following the current literature. I am delighted to be able to recommend the book.

Sherman Kupfer, M.D.
Mount Sinai School of Medicine

Abdominal Access in Open and Laparoscopic Surgery

Edmond K. M. Tsoi, M.D., Claude H. Organ, Jr., M.D. New York: Wiley-Liss, 1996. 189 pp. $98.00. ISBN 0-471-13352-3.

The surgical group at the University of California-Davis, EastBay Department of Surgery, have been pioneers in exploring the various possible uses of laparoscopy without an induced pneumoperitoneum with CO_2 gas. In this book, they follow up their 1993 book, “Gasless Laparoscopy With Conventional Instruments.” In this current book, they joined a few other colleagues to enlarge upon their experiences with this technique. In the early chapters, they present simple and brief reviews of various types of conventional open abdominal access for surgical procedures utilizing different incisional techniques and then move into the various types of laparoscopic abdominal access. They review the techniques of carbon dioxide pneumoperitoneum citing the advantages and disadvantages of carbon dioxide as the pneumoperitoneal gas. Next is a brief review of suggested placement of ports for various operative procedures, as advocated by several different authors. All of these techniques utilize standard carbon dioxide pneumoperitoneum techniques for laparoscopic surgery. They then review the use of low-pressure pneumoperitoneum, particularly in trauma cases and in enteral access. They allude briefly to the use of abdominal wall lift with low-pressure techniques and also mention the evolving use of the minilaparoscope in diagnostic laparoscopy. The complications associated with the use of carbon dioxide, namely hypercapnia, acidosis, increased airway pressure and the irritating effect of the gas on the peritoneum with local anesthesia, are all well known. A discussion follows of their experiences with alternative gases, namely nitrous oxide, helium, and argon. These views are expressed briefly and could profit from further discussion. Other complications of the use of carbon dioxide, such as misplacement of the inflation device, vascular and pulmonary complications, are reviewed.

The unique feature of this book is the review of the various types of abdominal wall-lifting devices, beginning with the wire techniques developed by Dr. Nagai in Japan. Dr. Nagai gives a fairly extensive description of his use of the technique in various surgical procedures, emphasizing his results in cholecystectomy. He mentions the problems associated with this technique, particularly in obese patients. Planar lifting is then described as exemplified by the Origin Laparofan®. This apparatus is a V-shaped fan retractor which is introduced through a periumbilical incision and is used to lift the abdominal wall via an attachment to a perpendicular electrically powered lifting column. This creates a trapezoidal space in the abdominal cavity rather than the spheroidal space created by the standard carbon dioxide pneumoperitoneum. There is also less compression of the abdominal contents. These are the disadvantages of this technique, but the disadvantages of the carbon dioxide pneumoperitoneum are eliminated. The plus side is the ability to use conventional instruments, the restoration of tactile sensation, and the lack of problems with maintenance of pneumoperitoneum. The applications of this technique in various surgical techniques are described briefly. In addition, the use of balloon dissecting instruments, particularly in retroperitoneal applications is also reviewed, again emphasizing the instruments developed by Origin Medsystems. These various devices are quite ingenious and promise to facilitate the use of "gasless" laparoscopy. In the closing chapters of the book, the pros and cons of gasless laparoscopy are discussed quite frankly, and the outlook for new and better techniques in laparoscopy are mentioned. I would like to have seen more extensive descriptions of various surgical procedures using this approach and some reporting of outcomes in a number of patients. It would also be useful to know how many other groups are using this approach.

The printing and photographs and drawings used in the book are good, but I did notice that, incredibly, the sketch on the front cover of the book diagramming laparoscopic cholecystectomy is reversed. All in all, I think this book outlines well the new and as yet underutilized technique of gasless laparoscopy and look forward to considerably further experience by these and other authors.

A. James McElhinney, M.D.
Mount Sinai School of Medicine

Crohn's Disease

Cosimo Prantera, Burton I., Korelitz, editors. New York: Marcel Dekker; 1996. 608 pp. $115.00. ISBN 0-8247-9410-9.

The first chapter of this book reveals immediately that this is not an ordinary textbook. Written by the eminent Dr. Henry D. Janowitz, Chapter 1 is an imaginary conversation between him and the three Mt. Sinai Hospital pioneers who described Crohn's disease—Burrill Crohn, Leon Ginzburg, and Gordon Oppenheimer. In their discussion, Dr. Janowitz reviews some advances since these clinicians first described the disease 63 years earlier and reports on areas of ongoing controversy, such as the role of colonoscopic surveillance for carcinoma and dysplasia in patients with long-standing Crohn's colitis. This chapter also establishes the pattern of a concluding commentary by an external reviewer, in this case the editor himself, Burton Korelitz.

This book is unique, in part because it is only the second book devoted solely to Crohn's disease. It is comprehensive in scope, elegant in writing, and practical in approach. The authors represent a *Who's Who* of investigators and practitioners in inflammatory bowel disease. The individual chapters are marked by clarity, organization, and common sense, and where included, the final commentaries put the chapter topics in perspective.

The book is divided into four sections. An introductory group of chapters deals with etiology and epidemiology. The second section describes the evaluation of the patient, including the role of radiography, endoscopy, and pathology, as well as patterns of disease and the thorny challenge of measuring disease activity. A noteworthy chapter by Dr. Korelitz compares and contrasts the role of barium x-rays and endoscopy in various clinical situations. The third section discusses principles of therapy, with individual chapters on aminosalicylates, corticosteroids, and immunosuppressants. The final section is entitled "Special Situations" and encompasses fully half of the chapters, with topics that include preventing relapses, the role of nutrition, pregnancy and fertility, psychosocial issues, extraintestinal manifestations, malignancy, and recent advances in pathogenesis and therapeutics.

If the book has a weakness, it is its organization. The order of the chapters is almost random in places. For example, the chapter on immunosuppressive therapy, hardly a first-line approach, precedes that on aminosalicylates. Prevention of relapse and recurrence is discussed under "Special Situations" but would be better placed in the section on therapy. The discussion of pathogenesis and epidemiology in the first section of the book gives short shrift to exciting recent advances in genetics, especially molecular genetics, and this thread is not picked up again until the last chapter of the book, an elegant overview of where the field is going, by Maria Abreu and Stephan Targan.

Organization aside, most chapters are gems. The writing is surprisingly even and the coverage quite appropriate and practical. I found the commentaries to be particularly useful, although inconsistent in their approaches. Some provide a well-annotated, scholarly overview, almost a recapitulation of the chapter, whereas others give a more concise synthesis that highlights the author's particular prejudices about a topic. Appropriately, no attempt is made to reconcile differing opinions among different chapters. For example, the use of ACTH for initial attacks of Crohn's disease is preferred over hydrocortisone by one author but not by another. In each case, the writer states his or her opinion clearly, marshals support for the point of view taken, and acknowledges the existence of divergent views. The best thing about the book is that you can find advice about how to handle virtually any problem in the management of a patient with Crohn's disease; none of the authors is shy about giving an opinion.

The book is strengthened by clear exposition and forceful writing. Some chapters have tables and some chapters, particularly those dealing with radiography, have excellent photographic examples. There are only a few photomicrographs of histologic material, which may disappoint readers who prefer a more visual approach.

Throughout the text, emphasis is placed on an historical perspective, in which the preeminent role of investigators from the Mount Sinai Hospital figures prominently. Indeed, despite the international array of experts with admirable contributions to this book, the accomplishments of investigators from Mount Sinai, described eloquently in Dr. Janowitz's introductory chapter, are graciously acknowledged throughout the text. "Crohn's Disease" serves as a fitting tribute to the institution which brought this disease to the attention of the world and which continues to play a vital role in uncovering the mysteries of its pathogenesis and optimal approaches to its management.

Lawrence S. Friedman, M.D.
Massachusetts General Hospital

Information for Authors

THE MOUNT SINAI JOURNAL OF MEDICINE, established in 1934 as *The Journal of the Mount Sinai Hospital,* is a peer-reviewed general medical journal. It is indexed or abstracted in *Index Medicus, Current Contents, Science Citation Index, Hospital Literature Index, International Nursing Index, Excerpta Medica, Chemical Abstracts, Biological Abstracts,* and major databases. Theoretical and basic science articles for the clinician, reviews, reports of clinical or research experience, articles on any subject affecting the practice of medicine, short notes in any specialty, book reviews, letters, and articles by medical students are welcome. The *Journal* generally follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals as revised in 1997 and modified by *The Journal* to conform to the style employed by it. The *Journal* aims at responding to authors of manuscripts within 8 weeks of submission.

Communications. Manuscripts and correspondence should be addressed to: Editor, *The Mount Sinai Journal of Medicine,* The Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Phone: (212) 241-6108; FAX: (212) 722-6386; e-mail: msjournal@msvax.mssm.edu.

Authorship Responsibility, Financial Disclosure, and Assignment of Copyright. Each author is required to sign (1) the statement on authorship responsibility; (2) the statement on financial disclosure; and (3) either the statement on copyright transfer or (4) the statement indicating that the author is or was a US government federal employee when this work was conducted and prepared for publication. These statements are printed from time to time on a page in the *Journal* entitled "Required Form for Authors" and can be photocopied for use. Copies may also be obtained from *The Journal's* office. Use additional copies of the form if there are more than six authors, and replace with the appropriate number of the author, e.g., 7th, 8th, etc. The signed original form(s) should be submitted with the manuscript.

Manuscript Preparation. Submit manuscripts in triplicate, including three sets of illustrations (see below). **Manuscripts must be typewritten or computer generated, double spaced throughout (including references, legends, and tables),** on one side of 8½ × 11 inch white bond paper with **one inch** margins. Other than the Title Page, the abstract page and each page containing text, legends, or tables should be numbered sequentially in the **top right corner,** and include a heading or header which identifies the last name of the first author in the **top left corner.** Begin a new page for the title page, abstract, initial page of text, references, each table, and legends. A floppy disk, if available, should accompany the manuscript. The label on the disk should specify the name of the first author, the title of the manuscript, how the disk has been formatted, and the word processing system used (DOS, Windows, or Windows 95). PC format is preferred but a high-density formatted Macdisk is acceptable. The text should be in ASCII, Microsoft Word or Wordperfect.

Drugs must be identified by their generic names. Do not use abbreviations on the title or abstract page. Define all abbreviations on first use in the body of the manuscript.

Any material taken directly from other sources must be accompanied by a written statement from both the author and publisher giving permission to *The Journal* for reproducing it. The authors must document in the manuscript that all clinical investigations described in the manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board or its equivalent. The text must indicate that the informed consent of each subject was obtained. If results of experiments on animals are reported in the manuscript, the text must indicate that these studies were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office or its equivalent which supervises such work.

Title Page. The title page must be double spaced, and not numbered. It should indicate (1) title of the article, phrased as concisely as possible; (2) first and last name of each author, middle initials, if any, and not more than two academic degree(s); (3) institutional affiliation and title or rank of each author; (4) name and address of department(s) and institution(s) from which the work originated; (5) the name and address (and voice and FAX telephone numbers if available) of the author who will receive and respond to correspondence; (6) the name and full postal address of the author from whom reprint(s) are to be requested; (7) acknowledgments of sources of grant support; (8) name, place, and date of any conferences at which some or all of the information was presented; and, (9) a running head of fewer than 40 letter spaces. At the bottom of the title page, *list 3 to 10 key words or phrases* to facilitate indexing in accord with Medical Subject Headings from Index Medicus. If more than one sheet is needed, label the supplemental sheet as Title Page ii.

Abstract. All articles must include an abstract on the first numbered page of the manuscript of not more than 250 words. Abstracts should be double spaced and divided into four paragraphs:

Background: what problem(s) was(were) addressed;
Methods: how the study was performed;
Results: the salient results;
Conclusions.

Key Words. Three to 10 key words or phrases must be provided at the bottom of the title page to facilitate indexing. (see above)

Units of Measurement. SI units are preferred, but values may be expressed in conventional units and conversion factors indicated. The range of normal values for the reporting laboratory must be indicated. When conventional units are used in figures or tables, the appropriate conversion factor(s) must be provided in legends or footnotes.

Editing. All papers will be edited to enhance conciseness and clarity without altering meaning and to ensure conformity with journal style. Authors whose primary language is not English should obtain help from someone proficient in English spelling and grammar.

Illustrations. Photographs, line drawings, and graphs should enhance understanding of the text. Three copies of each must be submitted with the manuscript. Line drawings and graphs should be professionally prepared or computer generated and camera ready. Symbols, lettering, and numbers should be large enough to remain easily legible after the figure has been reduced to fit the width of one column. Photographs must be sharp, high contrast, black and white glossy prints not exceeding 5 inches in height × 7 inches in width. The authors must pay attention to the quality of print reproductions of x-ray plates or transparencies to assure that the special features are labeled and will remain easily visible when reduced to fit the width of one column. The name of the subject and hospital number(s) should not be reproduced in the print. Black and white copies of photomicrographs are preferred and must be cropped to a width of 3⅛ inches. The type of stain and power of magnification must be indicated in the relevant legend. Electron photomicrographs should have internal scale markers. On the back of each print and photograph affix a gum label on which the number of the figure has been written to correspond to its identification in the text, title of manuscript, first author's last name, and the word "top" and arrow to indicate the top edge. **Do not write this information directly on the print and do not mount the print on cardboard.** Illustrations which are to appear together should be mounted accordingly as plates and should be equally sized. Protect the prints by enclosing them in cardboard and separate envelopes. **Do not use paper clips.**

Every effort should be made to avoid using a photograph which includes the face or part of the face of a subject. Facial

features should be marked to prevent identification of the subject unless the illustration carries details absolutely essential to the text. **In any case, a partial or full facial photograph of a subject will not be published unless written permission has been obtained from the subject and accompanies the photograph.**

Legends. Legends should not duplicate the text. Each should be on a separate sheet of paper and double spaced. Number each legend to match the illustration it describes. Illustrations mounted as plates to appear together should be accompanied by a single legend identifying the separate elements by position ("upper left," "middle") or by letters. If such illustrations have been labeled with letters, the same letters are to be used in the legend. The legend must indicate the magnification and type of stain used for photomicrographs.

Tables. Each table should be typed on a separate page, double spaced. Number tables consecutively (Table 1, etc.) to correspond to their appearance in the text. Give each table a brief title that is self-explanatory without reference to the text and type the title on a separate line below its number. Identify all abbreviations and/or symbols used in the table in a footnote.

References. All references cited in the text are to be numbered sequentially. Enclose the citation number in parentheses and place it before any punctuation, e.g., **Cytomegalovirus (1), steroids (2,3), and recreational drugs (4–6) have all been implicated (7).** Do not use superscripts. The reference list must be limited to works cited in the text, and numbered in the order in which they are cited. Journal title abbreviations must conform to those used in *Index Medicus.* The styles to be used for various kinds of citations to be listed in the section of the manuscript entitled References are illustrated in the version of "Uniform Requirements" published in the New England Journal of Medicine referenced below. The list of references must be typed, double spaced, on separate pages, following the arrangement and punctuation style as shown in the examples.

1. Brown LK. Sleep apnea syndromes: overview and diagnostic approach. Mt Sinai J Med 1994; 61:99–112.

2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336(4):309–315.

3. Couser WG. Glomerular diseases. In: Stein J. editor. Internal Medicine. 2nd ed. Boston: Little Brown; 1987. p. 834–861.

List the names of all authors when there are four or fewer. When there are five or more, list the names of the first three, then *et al.*

References to unpublished data (unless the information is In press) and personal communications should not be included in the list of numbered references. Instead, such information should be placed in the text in parentheses. Permission must be obtained from the appropriate individual to so quote the material. This permission must accompany the manuscript at the time of its submission. **If the manuscript is accepted for publication, the author(s) will be asked to confirm the accuracy of all references.**

Proofs. Proofs will be sent to the corresponding author as soon as they are available. Stylistic changes should not be made. Because of increased printing charges, the cost of author's alterations beyond routine correction of typographical errors in text and data will be billed to the author. Proofs should be corrected and returned to and received at the editorial office within 48 hours by express delivery at the author's expense to the address listed above ("Communications").

Offprint Orders. An offprint order form will be sent to the corresponding author with the proofs; if offprints are desired, the form must be returned to the editorial office, preferably with the proofs, but not later than 3 days to avoid late charges. A check for the exact amount in US dollars should be made out to the order of *The Mount Sinai Journal of Medicine.* Please indicate on the check the last name of the first author, and the title of the article. If for one reason or another, the offprint order form is not received with the proofs, it may be obtained directly from the editorial office via telephone or FAX. Offprints are available in minimum quantities of 100, at a cost depending on the number of printed pages and whether covers are desired. The cost of other than routine surface mail delivery, if requested, must be added to the cost of the offprints. Information on the cost of other than routine surface delivery can be obtained from the editorial office.

Required Form for Authors:

AUTHORSHIP RESPONSIBILITY, FINANCIAL DISCLOSURE, AND ASSIGNMENT OF COPYRIGHT

Article Title (type):

Each author must read and sign this form dealing with (1) authorship responsibility, (2) financial disclosure and (3) copyright transfer. An author who was a US federal employee when this work was conducted and prepared for publication, must sign statement (4) instead of statement (3).

1. Authorship Responsibility

I certify that I have participated sufficiently in the conception and design of this work, and the analysis of the data (where applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe that the manuscript represents valid work. I have reviewed the final version of the manuscript and approve it for submission for publication. Neither this manuscript nor one with substantially similar content under my (our) authorship has been published or is being considered for publication elsewhere, except as described in a separate attachment. Furthermore, I agree to produce the original recorded data on which the manuscript is based for examination by the Editor-in-Chief and/or his assignees should such records be requested.

2. Financial Disclosure

I certify that I do not have and have not had an affiliation or financial involvement with or in any organization or entity with a direct financial interest in the subject matter or materials being discussed in the manuscript (eg, employment, consultancies, stock ownership, honoraria), except as disclosed in a separate attachment.

Author(s) Signature(s) **Date**

1st ____________________

2nd ____________________

3rd ____________________

Author(s) Signature(s) **Date**

4th ____________________

5th ____________________

6th ____________________

3. Copyright

In compliance with the Copyright Revision Act of 1976, the signature of each author on this form shall indicate and be evidence of agreement and mutual understanding with *The Mount Sinai Journal of Medicine*, in consideration of the further action of the *Journal* to review and edit the manuscript being submitted, to transfer, assign, and convey all copyright ownership, including any and all rights incidental thereto, exclusively to *The Mount Sinai Journal of Medicine* if this work is published in the *Journal*.

Author(s) Signature(s) **Date**

1st ____________________

2nd ____________________

3rd ____________________

Author(s) Signature(s) **Date**

4th ____________________

5th ____________________

6th ____________________

4. US Federal Employees

I was an employee of the US federal government when this work was conducted and prepared for publication; therefore, it is not protected by the Copyright Act and copyright ownership cannot be transferred.

Author(s) Signature(s) **Date**

1st ____________________

2nd ____________________

3rd ____________________

Author(s) Signature(s) **Date**

4th ____________________

5th ____________________

6th ____________________

Return the original signed form to The Editor, The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, N.Y. 10029. Retain one copy of the form for your file. You may make as many photocopies as needed if your manuscript has more than six authors.

LEVY LIBRARY, MT. SINAI MEDICAL CENTER
3 4805 0488167 4

THE
MOUNT SINAI JOURNAL
OF MEDICINE

Forthcoming:

Grand Rounds

Money, Medicine and Methuselah
Christine K. Cassel
Mount Sinai School of Medicine

The Lactose Permease Meets Frankenstein: New Approaches to Membrane Protein Structure
H. Ronald Kaback
Howard Hughes Medical Institute
University of California
Los Angeles

Silicone Breast Implants and Connective Tissue Disease: An Overview
Harry Spiera and Robert F. Spiera
Mount Sinai School of Medicine

New Concepts in the Pathogenesis and Treatment of Allergic Asthma
Mitchell H. Grayson and Bruce S. Bochner
Johns Hopkins University
School of Medicine
Baltimore

Theme Issues

Computers in Medicine
Editors: Ray Cornbill and Joseph Kannry

Laparoscopy
Editors: Barry Salky and Michael Edye

Human Immunodeficiency Virus—AIDS
Editor: Henry Sacks

Issues in Hypertension
Editor: Clive Rosendorff

Reproductive Choice: Genetic Counseling and Assisted Reproductive Technology
Editors: Rosamond Rhodes, Daniel A. Moros, Allyson Robichaud

Available now:

Alumni Theme Issue Part A: Original Articles
Volume 63: Numbers 3&4, 1996: 134 pages. $20.00

Cross-Cultural Issues in Psychopharmacology and Part B: Alumni Theme Issue
Volume 63: Numbers 5&6, 1996: 154 pages. $20.00

THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 64 NUMBER 6 NOVEMBER 1997

CONTENTS

GRAND ROUNDS

Silicone Breast Implants and Connective Tissue Disease: An Overview *Harry Spiera and Robert F. Spiera* 363

The Utility of CT Scanning in Diagnosing Dementia *Barbara E. Cammer Paris* 372

Antiphospholipid Antibody Syndrome: An Acquired Cause of Venous and Arterial Hypercoagulability *Michelle Petri* 376

GENERAL ARTICLES

Acute Gouty Sacroiliitis: A Case Report and Review of the Literature *Bahar Bastani, Ravi Vemuri, and Mark Gennis* 383

Extended-Interval Dosing of Aminoglycosides *Michael E. Blam and Glenn S. Hammer* 386

Pediatrics at Mount Sinai *Donald Gribetz* 392

Current Trends in Onychomycosis Therapy: A Literature Review *David Hecker* 399

Anemia Secondary to Low Erythropoietin in a Patient with Normal Renal Function *Andre M. Kallab, Garbis Dabaghian, and Terenig Terjanian* 406

Screening for Lyme Disease in Hospitalized Psychiatric Patients: Prospective Serosurvey in an Endemic Area *Robert B. Nadelman, Edward Herman, and Gary P. Wormser* 409

The Imperative to Heal in Traditional Judaism *Fred Rosner* 413

continued inside

Veterans Affairs

THE MOUNT SINAI JOURNAL OF MEDICINE

The Mount Sinai Journal of Medicine is published by The Mount Sinai Medical Center of New York and has the following affiliates: Bronx Veterans Affairs Medical Center, New York; Elmhurst Hospital Center, Queens, NY; Queens Hospital Center, Queens, NY.

Editor-in-Chief

Sherman Kupfer, M.D.

Editor Emeritus

Lester R. Tuchman, M.D.

Associate Editors

Harriet S. Gilbert, M.D. Julius Wolf, M.D.

Administrative Assistant

Joseline Ilagan

Assistant Editor for Housestaff

Rochelle Waldman, M.D.
Michael E. Blam, M.D.

Assistant Production Assistant

Mel Meyer

Assistant Editors

David H. Bechhofer, Ph.D.
Constanin A. Bona, M.D., Ph.D.
Edward J. Bottone, Ph.D.
Lewis Burrows, M.D.
Christopher P. Cardozo, M.D.
Mark R. Chassin, M.D., MPH, MPP
Joseph S. Eisenman, Ph.D.
Richard A. Frieden, M.D.
Frederick Friedman, M.D.
Steven Fruchtman, M.D.
Paul L. Gilbert, M.D.
James N. Gladstone, M.D.
James H. Godbold, Ph.D.
Richard S. Haber, M.D.
Noam Harpaz, M.D.
Tomas Heimann, M.D.
Sheldon Jacobson, M.D.
Barry W. Jaffin, M.D.
Joseph L. Kannry, M.D.
Suzanne Carter Kramer, M.Sc.
Mark G. Lebwohl, M.D.
Zvi Lefkowitz, M.D.
Kenneth V. Lieberman, M.D.
Lynda R. Mandell, M.D., Ph.D.
Steven Markowitz, M.D.
Bernard Mehl, D.P.S.
Myron Miller, M.D.
Edward Raab, M.D.
Elliot J. Rayfield, M.D.
Allan Reed, M.D.
Clive Rosendorff, M.D., Ph.D.
Fred Rosner, M.D.
Allan E. Rubenstein, M.D.
David B. Sachar, M.D.
Henry Sacks, M.D.
Ira Sanders, M.D.
Martin H. Savitz, M.D.
Clyde B. Schechter, M.D.
Stuart C. Sealfon, M.D.
Michael Serby, M.D.
Phyllis Shaw, Ph.D.
Alex Stagnaro-Green, M.D.
Barry D. Stimmel, M.D.
Nelson Stone, M.D.
Max Sung, M.D.
Rein Tideiksaar, Ph.D.
Richard P. Wedeen, M.D.
Vincent B. Ziccardi, M.D., D.D.S.

Editorial Board

Barry S. Coller, M.D.
Barry Freedman, M.B.A.
Richard Gorlin, M.D.
Nathan Kase, M.D.
Panayotis G. Katsoyannis, Ph.D.
Charles K. McSherry, M.D.
Jack G. Rabinowitz, M.D.
John W. Rowe, M.D.
Alan L. Schiller, M.D.
Alvin S. Teirstein, M.D.
Rosalyn S. Yalow, Ph.D.

The Mount Sinai Journal of Medicine (ISSN No. 0027-2507; USPS 284-860) is published 6 times a year in January, March, May, September, October, and November in one indexed volume by The Mount Sinai Medical Center, Box 1094, One East 100th Street, New York, NY 10029-6574. Subscription price: individuals (U.S. and Canada), $75 per year; libraries and institutions (U.S. and Canada), $115 per year; individuals (outside U.S. and Canada), $100 per year; libraries and institutions (outside U.S. and Canada), $140 per year. Single copies $20. New subscriptions begin with the first issue of the calendar year. Send notice of change of address 60 days before its effective date. Periodicals postage paid at New York, NY and at additional mailing offices. POSTMASTER: Send address changes to The Mount Sinai Journal of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Telephone number (212) 241-6108; Fax (212) 722-6386. Copyright 1997 The Mount Sinai Hospital.

DISCLAIMER: The statement and opinions expressed in the *Journal* by authors and contributors are solely their own and not those of The Mount Sinai Medical Center or The Mount Sinai Journal of Medicine. All advertisements are expected to conform to ethical standards, and their appearance does not imply endorsement or approval by The Mount Sinai Medical Center and/or The Mount Sinai Journal of Medicine of the products with respect to effectiveness, quality, or safety. The Mount Sinai Medical Center and The Mount Sinai Journal of Medicine do not hold themselves responsible for statements made by the authors or contributors, and for any injury to persons or property which may have resulted from ideas, products, and services referred to in articles or advertisements.

COPYRIGHT: Material printed in the Journal is protected by copyright. In accord with U.S. Copyright law, no part of the Journal may be reproduced, displayed, or transmitted in any form, electronic or mechanical, including photocopying or by any information storage or retrieval system, without prior written permission to do so. Permission should be requested from The Editor. The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574.

THE
MOUNT SINAI JOURNAL
OF MEDICINE

Volume 64
Number 6
November 1997

CONTENTS *continued*

DERMATOLOGY NOTES

Onychomycosis vs Psoriasis *David Hecker* 417

Lyme Disease *Mark Lebwohl and Stephen Kurtin* 418

RADIOLOGY NOTES

Pulmonary and Skeletal Tuberculosis *Howard S. Blaustein and Maryanne Wysell* 419

BOOK REVIEWS

American Cardiology: The History of a Specialty and Its College *Leslie A. Kuhn* 420

Grief and AIDS *and* **Good Doctors, Good Patients, Partners in HIV Treatment** *Michael Teitelman* 421

Patient or Pretender: Inside the Strange World of Factitious Disorders *Berney Goodman* 423

What Works: Reducing Re-offending, Guidelines from Research and Practice *Charles Winick* 424

Comparative Vertebrate Neuroanatomy, Evolution and Adaptation *Marilyn Y. McGinnis* 425

The Handbook of Self-Concept: Developmental, Social and Clinical Considerations *Gary Rosenberg and Gary Holden* 426

Disorders of Personality: DSM-IV and Beyond *Richelle Kirrane* 427

Hives of Sickness, Public Health and Epidemics in New York City *Shalom Z. Hirschman* 427

Textbook on Psychiatric Epidemiology *S. L. Kushnir* 428

Pharmacology, Biology and Clinical Applications of Androgens: Current Status and Future Prospects. Proceedings of the Second International Androgen Workshop, Long Beach, California, February 17–20, 1995 *J. Lester Gabrilove* 429

continued

THE
MOUNT SINAI JOURNAL
OF MEDICINE

Volume 64
Number 6
November 1997

CONTENTS *continued*

List of Journal Reviewers in 1997 430
Author, Subject, Title Index to Volume 64 431
Information for Authors 437
Required Form 439

Silicone Breast Implants and Connective Tissue Disease:

An Overiew

Harry Spiera, M.D., and Robert F. Spiera, M.D.

Abstract

Silicone breast implants have been implicated in the possible pathogenesis of various connective tissue diseases. These findings have had a major impact not only on the medical and legal communities, but also on the community at large. In this communication, we review the history of the breast implant controversy, and examine the medical evidence regarding the possible link of silicone gel implants with connective tissue disorders such as scleroderma, rheumatoid arthritis, and lupus. Finally, we give a broad overview of the topic and offer some general suggestions regarding the care of patients who have silicone breast implants. **Key Words:** silicone breast implants, connective tissue disease, scleroderma

In 1962, Drs. Cronin and Girow performed the first silicone breast implant (1). Since that time, it has been estimated that more than 800,000 women have undersone this procedure (2). In most women, the procedure was for augmentation; in about 20%, it was done for reconstruction after mastectomy. In addition to its use in breast implantation, silicone has many other medical uses (3), including chin implants, testicular implants, and joint replacements. Silicone is also used in a variety of medical devices, including venous catheters, heart valves, silicone plugs for punctal occlusion, and pacemakers. Silicone is also used for lubricating syringes.

Since the early 1980s several publications have appeared suggesting a possible association between silicone breast implants and connective tissue diseases, particularly scleroderma (4–8). This possible association has generated a great deal of interest, not only in the medical community, but also throughout the legal profession, business world, and society at large.

In 1992, the Food and Drug Administration (FDA), after a review of possible health consequences of silicone breast implants, decided that further study was needed, and declared a moratorium on the implantation of silicone gel implants (9). They can now only be done in controlled situations with careful monitoring of the patients.

More than 13,000 lawsuits have already been filed against the manufacturers of the breast implants, as well as the companies that produce the silicone. Approximately 200,000 more people have reserved the right to undertake litigation in the future. Although a 4.2 billion dollar class action settlement has been offered (10), this amount is believed to be inadequate to cover the potential cost of the extant suits. Several individual multimillion dollar awards have further aggravated the situation. Dow Corning Corporation, the company which has produced most of the breast implants, has already petitioned for bankruptcy protection.

Amid the flurry of litigation, the services of lawyers, physicians, and clinical laboratories have been offered to patients. Moreover, several

---

From the Division of Rheumatology, Department of Medicine Mount Sinai School of Medicine, New York, NY. Address correspondence to Harry Spiera, M.D., Clinical Professor of Medicine, Chief, Division of Rheumatology, Department of Medicine, Mount Sinai School of Medicine, One East 100th Street, Box 1244 New York, NY 10029.

patient self-help groups have been organized which have focused on the putative health problems associated with silicone. This has been promulgated with meetings and newsletters. Meanwhile, the manufacturers of breat implants, chemical companies, and plastic surgerons have claimed that there are no data implicating the breast implants in the causation of connective tissue diseases. It has become very difficult for practicing physicians to advise their patients with breast implants about what action to take.

In 1988, we described five patients with scleroderma who had breast implants (7). In a case-controlled study comparing patients who have scleroderma and rheumatoid arthritis, the percentage of those having breast implants was far higher among the patients with scleroderma than those with rheumatoid arthritis, with a p value of less than 0.05. Since then, we have been involved with the issue and have seen almost 200 patients with silicone breast implants and rheumatic symptoms. In this communication, we present our own personal experience and a brief review of some of the relevant literature.

Chemistry and Biology Of Silicone

Silicon (Si) is the element with atomic number 14 on the periodic table. It has chemical properties similar to carbon and is located directly under carbon on the periodic table. Silica is silicon dioxide (SiO_2). Silica is found in the earth's crust and is a major component of both sand and quartz. It is one of the most common substances on the earth. Silicosis is a disease related to inhalation of silica particles causing fibrosis in the lungs. Silicones are a group of polymers made from silicon dioxide. The general formula is $CH_3(Si\text{–}O)_nCH_3$, with n representing the number of repeating units. Depending on the length of the polymer and degree of cross-linking, the physical properties of the silicone may range from the properties of a liquid to those of a semisolid. During the manufacturing process, various agents may be added to achieve certain desired physical properties. Among these are silica (SiO_2) and trifluoropropyl. Some evidence suggests that silicone *in vivo* may be degraded to silica (11).

Silicone was first used for medical purposes in 1947. It was used to waterproof dressings. Silicone eventually came into use in various implants based on the observation that silicone induced only minimal inflammatory responses in animals, and thus was both chemically and relatively biologically inert (12).

In early attempts at breast augmentation, silicone was injected directly into the breast tissue (13). Previously, attempts to use paraffin for this purpose led to unacceptable results, both in terms of local problems and serious systemic illness, including fatalities. When silicone was injected into breast tissue, many complications also ensued, including local granulomas, breakdown of tissue, and pulmonary complications (14–16). The injection of silicone into humans never received approval in the United States and is considered illegal. Nevertheless, this procedure was performed by several dermatologists in the United States in an attempt to remove wrinkles. Some of these patients suffered serious complications, including abscess formation, granulomas, and infection. In 1962, Drs. Cronin and Girow performed the first breast implant (1). This consisted of a silicone elastomer sac filled with a silicone gel material. It was assumed that the silicone gel would stay within the sac and that the gel would not leak into surrounding tissues. There is now extensive evidence that the silicone gel does indeed escape from the elastomer shell; silicone is frequently found outside the silicone elastomer capsule (17). This not only occurs when the capsule is ruptured (18), causing a leak of its contents, but can also result from a phenomenon called "bleeding" (19).

The theoretical considerations that silicone was both chemically and biologically inert and that the silicone gel did not escape the elastomer capsule led to the use of silicone breast implants. Extensive scientific evidence now reveals that neither of these assumptions is valid.

After the implantation of silicone breast implants, the elastomer capsule becomes coated with various proteins native to the host. Some of these proteins become rapidly denatured (3). These proteins may attract phagocytic cells, which results in an inflammatory response. Silicone joint implants also become coated with a connective tissue capsule. When silicone is injected into experimental animals, it is seen in several sites (20). Silicone particles are seen in white blood cells, demonstrating that they were phagocytosed. Moreover, silicone-containing material can be found in the skin, lymph nodes, lungs, and synovium of patients with breast implants (21, 22).

Silicone taken from a breast implant may enhance the antibody response in experimental animals to bovine serum albumin (23). This suggests that the silicone behaves as an adjuvant. These and many other studies have clearly demonstrated that silicone and silicone gel indeed have biological effects. It is certainly not clear, however, that these biological effects are harmful to the host.

There are many materials being used for medical purposes which are not totally biologically inert. Among these are the various metals and plastics used for joint replacement, heart valves, and vascular grafts.

The second assumption underlying the utilization of silicone gel-filled elastomer envelopes for breast augmentation was that the silicone gel would remain within the elastomer capsule. As noted above, it has been amply demonstrated that the gel does leak through the elastomer membrane in varying proportions into the connective tissue capsule that forms around the implant. It has also been demonstrated that silicone is found in more distant sites.

Complications of Breast Implants

Complications of breast implant surgery that have been described (24) include rupture of the elastomer membrane, contraction of the connective tissue capsule that forms around the implant, infection, pleural effusion, and chest wall pain. These complications will not be discussed in this communication. Although capsular rupture and contraction and local infection clearly can be ascribed to the implants, the situation is not quite so clear when the patient has had an implant and develops a connective tissue disease.

Connective Tissue Diseases After Cosmetic Surgery

The initial descriptions of connective tissue diseases complicating silicone breast augmentation came from Japan in 1984. Kumagai et al. (6) reviewed the Japanese experience with connective tissue diseases arising after cosmetic surgery. The patients, who had received injections of either paraffin or silicone directly into their breast tissue, included 18 patients of their own, and another 28 patients described in the medical literature. More than half of these patients had a clearly defined connective tissue disease, most of which was scleroderma and its variants. Rheumatoid arthritis, systemic lupus, and polymyositis were seen less frequently. Some had what the authors described as "human adjuvant disease" in which patients had fever, arthralgias, skin rashes, and various blood abnormalities.

In 1982, Van Nunen et al. (5) described several patients with breats implants, one with lupus, one with mixed connective tissue disease, and another with rheumatoid arthritis and Sjogren's syndrome. There have been many other reports of connective tissue disease arising in patients who have previously had silicone breast implants. In 1988, we reported on five patients with scleroderma who had breat implants (7). The patients were from a consecutive series of 106 women with scleroderma who had been seen by us. During that same period, we saw 286 women with rheumatoid arthritis, only one of whom had a breast implant. The difference was statistically significant with a p value of less than 0.05. This suggested that there was a possible association between breast implants and scleroderma. After this report was published, a large number of reports appeared linking the breast implants with a variety of connective tissue diseases, including scleroderma, rheumatoid arthritis, lupus, Sjogren's syndrome, and a variety of fibromyalgia-like illnesses (25). In addition, several neurological syndromes have been reported (26), including diseases resembling multiple sclerosis, peripheral neuropathy, and amyotrophic lateral sclerosis. Diffuse pulmonary fibrosis and primary biliary cirrhosis (27) have also been described.

Personal Series

We have seen 186 patents who had silicone implants who subsequently developed rheumatic symptoms (Table 1). Patients were referred either by physicians or other patients. No lawyer-initiated referrals have been accepted.

Of the 186 patients who were seen, 182 had silicone breast implants, whereas two others had implants of silicone to augment their chins and two had free silicone injected.

Of the entire group, 64 (34.4%) had a definable connective tissue disease: 17 had scleroderma, 2 morphea, 11 overlap syndromes, 8 rheumatoid arthritis, 5 Sjogren's syndrome, 3 dermatomyositis/polymyositis, 6 polymyalgia rheumatica, 3 systemic lupus, 2 pulmonary fibrosis, and 1 each with palindromic rheumatism, discoid lupus, psoriatic arthritis, peripheral neuropathy, pleural effusions, sarcoidosis, thrombotic thrombocytopenic purpura (TTP), and antiphospholipid syndrome. The other patients included individuals with fibromyalgia, degenerative joint disease, soft tissue rheumatism, and two with metastatic bone disease.

Among those patients with an objectively demonstrable connective tissue disease, the duration between insertion of the implant and the appearance of the connective tissue disease ranged from as short as 6 months for TTP to 26 years for one of the patients with scleroderma.

TABLE 1
Rheumatic Disease in 186 Women with Silicone Implants

Diagnosis	*n*
Scleroderma	19
Systemic	17
Morphea	2
Overlap syndrome	11
Rheumatoid arthritis	8
Polymyalgia rheumatica	6
Sjogren's Syndrome	5
Lupus	4
Systemic	3
Discoid	1
Polymyositis/dermatomyositis	3
Pulmonary fibrosis	2
Psoriatic arthritis	1
Palindromic rheumatism	1
Sarcoidosis	1
Antiphospholipid syndrome	1
Peripheral neuropathy	1
Thrombotic thrombocytopenic purpura	1
Fibromyalgia-like syndrome	57
Osteoarthritis	46
Soft tissue rheumatism	15
Metastatic carcinoma	2
Facial swelling	1
Skin abscesses	1

n = number of patients.

There have been seven deaths. Of patients with scleroderma one died of hypertensive renal crisis, one of pulmonary fibrosis, and one of cardiac arrhythmia. All three of these patients had their breast implants removed. One patient with scleroderma and a chin implant died of progressive congestive heart failure approximately 1 year after the implant was removed. Two patients with dermatomyositis/polymyositis died. They both had rapidly progressive myositis resistant to treatment, and the removal of the implant from one had no discernible effect. The patient with TTP died despite vigorous treatment, including removal of the prosthesis. Thus, of the seven patients who have died, the implants were removed in six. The removal of the implants did not seem to have any discernible effect on the course of the connective tissue disease in these patients (28).

In one patient with breast implants and scleroderma, there was an improvement of the tightening of the skin and arthralgias, as well as improvement in pulmonary diffusing capacity after the implants were removed. In another patient with breast implants and scleroderma, removal of the implants was associated with an apparent improvement of her skin disease. However, 3 years after the removal of the implant, this patient developed hypertensive renal crisis which has been controlled with converting enzyme inhibitors. One patient with a pleural effusion has had silicone particles detected in the pleural fluid (29). Patients with fibromyalgia-like illnesses have not had any major change in their clinical course, whether the implants were or were not removed.

Review of the Medical Literature

The medical literature includes several different types of studies. There are a large number of isolated case reports or short series describing the appearance of a connective tissue disease in patients with breast implants. There have also been groups of cases presented by investigators working in a single institution.

The earliest case control study is the one we previously alluded to, published in 1988, showing the increased frequency of breast implants among patients with scleroderma as opposed to those with rheumatoid arthritis (7).

Surveys of large groups of patients have been carried out to determine whether there is a greater frequency of connective tissue disease among patients with implants as opposed to controls (30, 31). These were conducted primarily by phone or by mail. There also have been several studies which measured various antibodies such as antinuclear antibodies or rheumatoid factor in patients with breast implants.

A recently published study (32) of a large group of nurses demonstrated that although there was not a major risk of connective tissue diseases among recipients of silicone breast implants, there was a consistent statistical increase of connective tissue disease among those nurses who had implants as opposed to those who did not. The relative risk overall was 1.25. The relative risk of scleroderma was 1.86. The study concluded that although there was no *major* health hazard from the implants, there was indeed an increase in connective tissue diseases.

Antinuclear antibodies (33, 34) with varying specificity have been found among patients with breast implants. This occurred whether the patients had associated connective tissue disease or not (35). The significance of this type of finding is unclear.

There has been no entirely specific antibody found. Autoantibodies found in patients with connective tissue disease and breast implants have had the same pattern of autoantibody production as in the naturally occurring group. Thus, the extant medical literature seems to support the contention that although there is a slight increase in the risk of connective tissue disease among breast implant recipients, the overall risk is rather low.

Studies of immunogenetics have revealed that among patients with breast implants who have dermatomyositis, there is an increased frequency of an HLA DR subset as opposed to other patients with naturally occurring dermatomyositis (36). In contrast to this, Morse et al. (37) have demonstrated that among patients with scleroderma who have breast implants, the immunogenetic typing is similar to those patients who have not had implants. The issue of whether women with particular genotypes are predisposed to disease when exposed to silicone remains unanswered at this time.

"Siliconosis"

Most patients with breast implants who report rheumatic symptoms do not have a "classic" or typical connective tissue disease, such as rheumatoid arthritis, systemic lupus, Sjogren's syndrome, scleroderma, dermatomyositis/polymyositis, or mixed connective tissue disease. They usually complain of fatigue, arthralgia, myalgia, subjective xerostomia, cognitive disturbances, and generalized malaise. These patients have a dearth of physical findings and very rarely have objective abnormalities. Some physicians have labeled this as a new clinical syndrome which they call "siliconosis" (38). These patients, however, are very similar to those described as having chronic fatigue syndrome, fibromyalgia, Gulf War Syndrome, Icelandic disease, and "multiple chemical sensitivities." In the absence of objective findings, it is very difficult to evaluate these patients, particularly in an atmosphere of litigation.

Regulatory Issues

The use of free silicone injection never received FDA approval in the United States. This followed the problems experienced with such injections in Japan.

After breast implants were first introduced in the 1960s, they were not subject to regulation. However, in 1991, after the flurry of case reports of various health problems associated with the breast implants, the FDA imposed a moratorium on their further use. Since that time, only selected patients could get the silicone implants, and only after registration and careful observation. Saline-filled implants are still being used. Other surgical procedures for breast reconstruction, particularly using the patient's own tissue, have found some acceptance.

Legal Issues

As this article was being written, the litigation process was still active. There have been numerous litigants in the class action suit, although many others have opted out of the settlement. For the class-action suit, an offer of 4.2 billion dollars has been made to settle the claims, but given the number of claims already filed and those potentially to be filed, it is probably inadequate to settle the claims. As a result, Dow Corning, the manufacturer of most of the implants, has filed for bankruptcy protection. More recently, the Dow Chemical Company has also been made the target of lawsuits.

To this date, the litigation has been focused primarily on silicone used for breast implants, although claims have been made against some of the other silicone uses as well. It is likely that such claims will increase.

Other Materials

It seems unlikely at this point that the drug and chemical companies will attempt augmentation or reconstruction with other forms of chemical devices. This is primarily because of the legal climate.

Relevant Questions

For the practicing physician, there are several questions that need to be answered:

1. Is there an increased frequency of connective tissue diseases among patients with breast implants?
2. If so, what are the diseases?
3. Is there a unique disease associated with breast implants?
4. What is the effect of removing the implant on the clinical course of the disease?
5. How should the diseases be treated?
6. Are there any predisposing factors as to why some patients would get the disease and others would not?
7. If there is an association, what would be the putative pathogenetic mechanism?

Increased Frequency of Connective Tissue Diseases

It is not clear whether there is an increased prevalence of connective tissue diseases among patients with breast implants. In two major studies, the results seem to have been negative. In a study from Olmstead County in Minnesota, 749 women had received breast implants (30). For each patient, two control patients were chosen. Only 5 of the 749 patients with breast implants eventually developed connective tissue disease. Two had polymyalgia rheumatica, one had Sjogren's syndrome, one had polychondritis, and one had the arthritis associated with inflammatory bowel disease. In 10 of the 1128 community control patients, there were three with ankylosing spondylitis, two with rheumatoid arthritis, and two with vasculitis. That study can be criticized based on several major issues. One is the low prevalence of rheumatoid arthritis in the series, that is 0.08%, an order of magnitude lower than that found in most series (39). This raises the question of whether this was indeed a representative community or whether the true frequency of rheumatic diseases had been underdiagnosed in this population. Further, the numbers available for the study were too few to detect an increased frequency of a disease such as scleroderma. Indeed, there was no scleroderma found in any of the patients, either in the implant or the control group. If it is assumed that the frequency of scleroderma in the general population is 50 per million (40), and that breast implants increased the frequency by 3-fold, it would require the study of 44,000 women with breast implants and 44,000 control subjects without breast implants to demonstrate such a difference of this extent. No study of this magnitude has been done.

The second study addressed the question by surveying nurses in the Nurses Health Study (32). Of 109,758 surveyed, 89,376 returned the questionnaire, and 88,159 answered questions related to breast implants. Of those surveyed, 1,861 had some type of breast augmentation. Connective tissue disease was confirmed in 516 subjects (0.06% of the 87,500 surveyed). Three of the 516 with connective tissue disease had breast implants, all with rheumatoid arthritis. No scleroderma, polymyositis, or Sjogren's syndrome was found in the breast implant group. The major criticism of this study was that it did not have the power to find an increase in a rare disease such as scleroderma or dermatomyositis. Indeed, the data could be taken to suggest that breast implants may protect against connective tissue disease.

Types of Disease

In all clinical series of patients with breast implants and connective tissue disease, a consistent finding is that scleroderma is the most frequent of the identifiable connective tissue disease (41). If epidemiologists were to enter a community and scleroderma was found to be more frequent than rheumatoid arthritis or systemic lupus, major investigations would be undertaken. The overrepresentation of scleroderma in all the published series has never been adequately explained. Moreover, the total number of patients with scleroderma already reported in the extant medical literature exceeds the number that would be expected by chance alone. Given the observation that the latent period between breast implantation and dvelopment of scleroderma can be more than 20 years, it is quite likely that there are many patients with breast implants and scleroderma who have not been reported in the medical literature.

Of all the connective tissue diseases, it is scleroderma which is most frequently related to some environmental abnormality (42). Included are the association between scleroderma and exposure to silica, various organic materials, the toxic oil syndrome, and eosinophilia myalgia syndrome (EMS) related to tryptophan. For no other well-defined connective tissue disease is there such evidence.

Unique Disease

Most of the patients entering litigation reported a syndrome that has been referred to as “siliconosis.” The major symptoms include fatigue, neuralgias, myalgias, and cognitive disturbance, as well as subjective dry mouth. As far as serological abnormalities, there have been some reports of increased IgM and antinuclear antibodies (43). These patients have been reported to have a high incidence of breast capsule contracture or actual rupture. Some attempts have been made recently to attempt to formulate criteria for “siliconosis,” or systemic silicone-related disease (44, 45).

It is difficult to separate the patients with “siliconosis” from fibromyalgia or what is called chronic fatigue syndrome (46). In an atmosphere of litigation and recrimination, it is very difficult to study patients. It has been pointed out that in the presence of litigation, criteria for fibromyalgia have never been adequately tested (Wolf F, personal communication).

In our own experience with more than 180 patients referred by standard referral patterns, most patients who have articular complaints have fibromyalgia. In a retrospective chart review, we found that every time that we had seen a patient with breast implants and fibromyalgia-like syndrome, in the same week we saw at least one patient with fibromyalgia who never had breast implants. We do not believe that there is a unique disease associated with silicone gel implants.

It will take years of careful observation, both clinically, biochemically, and pathologically, before the issue can be resolved. Hopefully, when the present flurry of litigation has subsided, better answers will be forthcoming.

Implant Removal and Alteration of Disease Course

Whether the removal of the implants alters the natural course of the connective tissue disease associated with breast implants is difficult to answer, as there are very few hard data. In our personal experience with breast implants and identifiable connective tissue disease, explantation has not seemed to have any consistent effect. As noted above, of the seven patients who died, the implants had been removed from six. Vasey et al. (47) reported that some women whose implants had been removed subsequently showed improvement. Those reports apply mainly to patients who had the fibromyalgia-like symptoms.

In our personal experience, 30 patients with a fibromyalgia-like syndrome were surveyed by mail to see what occurred in their disease (unpublished observations). Twenty of those who had responded had the implants removed. In 16, there was no difference, and of the four remaining, two had improvement in symptoms, whereas two deteriorated.

If silicone did indeed cause rheumatic symptoms, it would not be due to the material in the elastomer sac, but rather due to what had already escaped and was in contact with the host's immune system. It might therefore be somewhat unreasonable to expect that removal of the implant alone, without removing the silicone that had already escaped, would result in major improvement.

The important question, of course, is how to advise the patient who has a silicone breast implant and who is suffering from rheumatic symptoms. We take the following approach. We explain to her the nature of the evidence. Here we assume that the patient is happy with the cosmetic result of the implant and that there are no other complications, such as contracture, rupture, chest wall pain, or infection. If the patient has a mild illness in which symptoms can be treated with relatively simple means such as a nonsteroidal anti-inflammatory agent or an antimalarial agent, then it is reasonable to keep the implants in place. If, on the other hand, the patient has a life- or organ-threatening disease, or one that requires very aggressive treatment, such as high-dose corticosteroids or immunosuppression, then we would advise removal of the implant to see if any improvement ensues.

It must be remembered that removal of the implants is not a trivial issue. It involves an operation that requires general anesthesia and is quite bloody. The connective tissue capsule forming around the implant must be carefully dissected (48) and removed. Furthermore, after such a procedure, the patient is often left with less breast tissue than she initially had before the breast implant. The psychological consequences of removing an implant can be most serious. In this situation the question arises as to whether a saline-filled implant should be inserted. We have taken the position that if indeed the silicone is causing health difficulties, we do not know whether it is caused by the silicone gel inside the implant or the silicone elastomer shell. At this time, it does not seem to make much sense to subject the patient to a significant surgical procedure to remove silicone and then to put more silicone in.

Putative Mechanism

If a connective tissue disease such as scleroderma results from implantation of silicone, several possibilities could be considered. As suggested by Kumagai et al. (6), silicone could probably act as an "adjuvant," increasing the immunogenicity of normal tissues. There is indeed evidence that silicone can act as an adjuvant.

A more likely possibility, however, is that silicone particles could be ingested by macrophages which in turn could produce cytokines which could induce fibrosis. This indeed has been the postulated mechanism of the fibrosis occurring in silicosis (49). The human body has no mechanism to clear silicone particles. Once ingested by the macrophage, it stays in the body even when the macrophage dies; the silicone is reingested, and the cycle continues with more fibrosis both locally and distally.

Predisposing Factors

There has been only two studies relevant to this issue. Love et al. (36) examined patients with dermatomyositis who had breast implants, and they found an increased frequency of the MHC HLA-DQA1 * 0102 allele as compared with the general population. On the other hand, Morse et al. (37) studied a group of patients with scleroderma who had breast implants and had basically the same genotype as those with naturally occurring disease.

Summary and Conclusion

The relationship between silicone implants and connective tissue disease is still unclear.

There is no evidence that classic systemic lupus or rheumatoid arthritis is increased. There is some evidence, however, which suggests that scleroderma occurs in a greater frequency among the recipients of silicone implants than might be expected by chance. There is also ample evidence that scleroderma is often associated with some environmental agents.

The question of whether breast implants might cause a unique syndrome remains controversial. Because no objective guidelines exist to evaluate these patients, and the climate of litigation confounds the problem, there is not enough scientific evidence to answer this question.

The decision as to what to recommend to a woman who has connective tissue disease and breast implants must be individualized in the context of the severity of the disease and its prognosis. In addition, the risks and disadvantage of explantation must be considered. Which of the alternative treatments alone or in combination is best is unsettled. Resolution will require more experience and definitive data.

References

1. Cronin TD, Gerow FJ. Augmentation mammoplasty: A new 'natural feel.' Excerpta Med 1964; 44–49.
2. Cook RR, Delongchamp RR, Woodbury M, et al. The prevalence of women with breast implants in the United States—1989. J Clin Epidemiol 1995; 48:519–525.
3. Tang L, Eaton JW. Inflammatory responses to biomaterials. Am J Clin Pathol 1995; 103:466–471.
4. Brozena SJ, Fenske NA, Cause CW, et al. Human adjuvant disease following augmentation mammoplasty. Arch Dermatol 1988; 124:1383–1386.
5. Van Nunen SA, Gatenby PA, Basten A. Post mammoplasty connective tissue disease. Arthritis Rheum 1982; 25:694–697.
6. Kumagai Y, Shiokawa U, Medsger TA, Rodnan GP. Clinical spectrum of connective tissue disease after cosmetic surgery: observations on 18 patients and a review of the Japanese literature. Arthritis Rheum 1984; 27:1–12.
7. Spiera H. Scleroderma after silicone augmentation mammoplasty. JAMA 1988; 260:236–238.
8. Bridges AJ, Conley C, Wang G, et al. A clinical and immunological evaluation in women with silicone breast implants and symptoms of rheumatic disease. Ann Intern Med 1993; 118:929–936.
9. Estes EH. Breast implants. Report of the Council on Scientific Affairs, Resolution 259, A-91, Jan 1992.
10. Kolata G. Implants: courts dispose while science unfolds. The New York Times 1994 Jun 19.
11. Wilkerson P. General silicone chemistry. Distributed communication to FDA advisory panel. February 1992.
12. Blocksama R, Braley S. The silicones in plastic surgery. Plast Reconstr Surg 1965; 35:366–370.
13. Furiri M, Kubota A, Kobayashi A. Adverse effects after breast augmentation: systemic reactions by foreign substance injecton. Keisei Geka 1974; 36:1371–1375.
14. Sergatt TS, Limoc SP, Baldwin CM Jr, Laub DR. Human adjuvant disease, possible autoimmune disease after silicone implantation: a review of the literature, case studies, and speculation for the future. Plast Reconstr Surg 1986; 78:104–114.
15. Endo LP, Edwards NL, Longley S, et al. Silicone and rheumatic disease. Semin Arthritis Rheum 1987; 17: 112–118.
16. Baldwin CM Jr, Kaplan EN. Silicone-induced human adjuvant disease. Ann Plast Surg 1983; 10:170–273.
17. Windig O, Christensen L, Thompsen JL, et al. Silicone in human breast tissue surrounding silicone breast prostheses: a scanning electron microscopy and energy-dispersive x-ray investigation of normal, fibrocystic, and peri-prosthetic breast tissue. Scand J Plast Reconstr Surg Hand Surg 1988; 22(2):127–130.
18. Capozzi A, DuBois R, Pennisi VR. Distant migration of silicone from a ruptured breast implant. Plast Reconstr Surg 1978; 62:302–303.
19. Barker DE, Retsky MI, Schultz S. "Bleeding" of silicone from bag-gel breast implants and its clinical relation to fibrous capsule reaction. Plast Reconstr Surg 1978; 62: 836–841.
20. Teuber SS, Yoshida SH, Gershwin ME. Immunopathologic effects of silicone breast implants. West J Med 1995; 162:418–425.
21. Silver RM, Sahn EE, Allen JA, et al. Demonstration of silicon in sites of connective-tissue disease in patients with silicone breast implants. Arch Dermatol 1993; 129: 63–68.
22. Edmond JA, Versaci AD. Late complications of closed compression capsulotomy of the breast. Plast Reconstr Surg 1980; 66:478–479.
23. Naim JO, Lazafame RJ. The adjuvant effect of silicone-gel on antibody formation in rats. Immunol Invest 1993; 22:151–161.
24. Steinbach BG, Hardt NS, Abbitt DL et al. Breast implants, common complications, and concurrent breast disease. Radiographics 1993; 13:95–118.
25. Houpt KR, Sontheimer RD. Autoimmune connective tissue disease and connective tissue disease-like illnesses after silicone gel augmentation mammoplasty. J Am Acad Dermatol 1994; 31:626–642.
26. Shoaib BO, Patten BM, Cackins DS. Adjuvant breast disease: an evaluation of 100 symptomatic women with breast implants or silicone fluid injections. Keio J Med 1994; 43:79–87.
27. Brautbal N, Vojdani A, Campbell AW. Silicone breast implants and autoimmunity: causation, association, or myth? Toxicol Ind Health 1992; 8:231–237.
28. Spiera H, Kerr LD. Scleroderma following silicone implantation: a cumulative experience of 11 cases. J Rheum 1993; 20(6):958–961.
29. Hirmand H, Hoffman LA, Smith SP. Silicone migration to the figural space associated with silicone-gel augmentation mammoplasty. Ann Plast Surg 1994; 32:645–647.
30. Gabriel SE, O'Fallon WM, Kurland LT, et al. Risk of connective-tissue diseases and other disorders after breast implantation. N Engl J Med 1994; 330:1697–1702.
31. Sanchez-Guerrero J, Coloditz GA, Karlson EW, et al. Silicone breast implants and the risk of connective tissue diseases and symptoms. N Engl J Med 1995; 332:1666–1670.
32. Hennekens CH, Lee IM, Cook NF, et al. Self-reported breast implants and connective tissue disease in female health professionals: a retrospective cohort study. JAMA 1996; 225(8):616–621.
33. Cuellar ML, Scopelitis E, Tenenbaum SA, et al. Serum

antinuclear antibodies in women with silicone breast implants. J Rheumatol 1995; 22:236–240.

34. Bridges AJ. Autoantibodies in patients with silicone implants. Semin Arthritis Rheum 1994; 24 Suppl 1:54–60.
35. Morse JH, Spiera H. Autoimmune diseases, immunoglobulin isotypes and lymphocyte subsets in 30 females with breast augmentation mammoplasty [abstract]. Arthritis Rheum 1992; 35:565.
36. Love LA, Weiner SR, Vasey FB, et al. Clinical and immunogenetic features of women who develop myositis after silicone implants (MASI) [abstract]. Arthritis Rheum 1992; 35 Suppl 9:S46.
37. Morse JH, Fotino M, Zhang Y, et al. Position 26 of the first domain of the HLA-DQB1 allele in post-silicone implant scleroderma. J Rheumatol 1995; 22:1872–1874.
38. Solomon G. A clinical and laboratory profile of symptomatic woman with breast implants. Semin Arthritis Rheum 1994; 24(1 Suppl 1):29–37.
39. Silman AJ, Hochberg MC. Epidemiology of the rheumatic diseases. New York: Oxford University Press; 1993. p. 14.
40. Silman AJ, Jannini S, Symmons D, Bacon P. An epidemiological study of scleroderma in the West Midlands. Br J Rheumatol 1988; 27:286–290.
41. Spiera R, Gibofsky A, Spiera H. Silicone breast implants and connective tissue disease: an overview. J Rheumatol 1994; 21:239–245.
42. Silman AJ, Hochberg MC. Epidemiology of the rheumatic diseases. New York: Oxford University Press; 1993. p. 206.
43. Solomon G. Clinical features of a subset of symptomatic women with silicone breast implants and extreme elevations of serum IgM [abstract]. Arthritis Rheum 1996; Suppl 9:S52.
44. Colin M, Borenstein D, Espinoza L, et al. Analysis preliminary operational criteria for systemic silicone related disease (SSRD) [abstract]. Arthritis Rheum 1996; 39 Suppl 9:S51.
45. Silverman S, Borenstein D, Solomon G, et al. Preliminary operational criteria for systemic silicone related disease (SSRD) [abstract]. Arthritis Rheum 1996; 39 Suppl 9:S51.
46. Chow HY, Cash JM, Calabrese LH, Wilke WS. Patients with chronic fatigue syndrome (CFS) and silicone-associated illness (SAI) are similarly disabled [abstract]. Arthritis Rheum 1996; 39 Suppl 9:S52.
47. Vasey FB, Havice DL, Bocanegra TS, et al. Clinical findings in symptomatic women with silicone breast implants. Semin Arthritis Rheum 1994; 24 Suppl 1:22–28.
48. Copeland M, Kressel A, Spiera H, Herman G. Bleweis is systemic inflammatory disorder related to fibrous breast capsule after silicone implant removal. Plast Reconstr Surg 1993; 92:1179–1181.
49. Reiser KM, Last SA. Silicosis and fibrogenesis: fact and artifact. Toxicology 1979; 13:51–72.

The Utility of CT Scanning in Diagnosing Dementia

Barbara E. Cammer Paris, M.D.

Abstract

Dementia is an illness that affects an estimated 10% of noninstitutionalized persons older than 65 years of age. Among those older than 85 years of age, dementia is estimated to affect 20 to 50% of the population. The diagnosis of Alzheimer's disease is based on clinical criteria and the exclusion of other causes of dementia. Neuroimaging procedures, mostly CT scans, have been used to exclude other lesions presenting as dementia. The yield of these procedures has been estimated to be about 3%. This article reviews some of the literature on this topic in an effort to establish specific recommendations for neuroimaging procedures in patients who present with dementia. **Key Words:** Alzheimer's disease, dementia, CT scanning.

THE PREVALENCE OF SENILE DEMENTIA of the Alzheimer's type dramatically increases with age. Dementia affects 3 to 11% of noninstitutionalized adults older than 65 years of age (1). About 10% of persons aged 85 to 88 years develop Alzheimer's disease each year (2). The onset is often insidious, followed by a gradually progressive course lasting from 1 to 15 years. A diagnosis of Alzheimer's disease can be made based on clinical criteria (3), often in a patient with multiple comorbidities. Based on well-defined clinical criteria for diagnosing Alzheimer's disease and the relative rarity of other clinically relevant illnesses presenting in the same fashion, do all patients who meet these clinical criteria need a CT scan to rule out the other less common causes of dementia? What potentially reversible conditions might be uncovered by CT scan of the brain and with what frequency? How can a CT scan make a difference?

Diagnosis

The American Psychiatric Association's Diagnostic Criteria for Alzheimer's Dementia are listed in Table 1. Key to the diagnosis is the loss of cognitive and emotional abilities, which interferes with daily functioning, in addition to memory impairment. These patients are distinctly different from healthy patients of advanced age who demonstrate only a decline in cognitive function, most notably in the areas of psychomotor and executive function, memory, and category verbal fluency. Corey-Bloom and colleagues (4) performed neuropsychological testing on a cohort of normal elderly and found that the group older than age 85 demonstrated a decline in cognitive function compared with the younger cohort, aged 65 to 84 years, but this was not accompanied by a functional impairment. In addition, in making a diagnosis of Alzheimer's disease, it is important to exclude other causes of dementia. The differential diagnosis of dementia is conveniently categorized by the mnemonic D-E-M-E-N-T-I-A, as follows: Drugs; Emotional illness including depression; Metabolic/endocrine disorders; Eye/ear/environment; Nutritional/neurologic including some vascular and structural brain lesions such as hydrocephalus; Tumors/trauma including metastatic and primary brain tumors, subdural hematomas; Infection; Alcohol/anemia/atherosclerosis.

Alzheimer's disease can be subdivided into three stages: early, intermediate, and severe. Symptoms of early-stage disease are often over-

---

Adapted from a presentation at Grand Rounds, Department of Medicine, Mount Sinai School of Medicine, on September 24, 1996.

Address correspondence to Barbara E. Cammer Paris, M.D., Clinical Associate Professor of Geriatrics and Medicine, One East 100th Street, Mount Sinai School of Medicine, Box 1070, New York, NY 10029.

TABLE 1

Diagnostic Criteria for Dementia of the Alzheimer's Type

A. The development of multiple cognitive deficits manifested by both
  1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
  2. One (or more) of the following cognitive disturbances:
    a. Aphasia (language disturbance)
    b. Apraxia (impaired ability to carry out motor activities despite intact motor function)
    c. Agnosia (failure to recognize or identify objects despite intact sensory function)
    d. Disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social and occupational functioning and represent a significant decline from a previous level of functioning.
C. The course is characterized by gradual onset and continuing cognitive decline.
D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
  1. Other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor).
  2. Systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection).
  3. Substance-induced conditions.
E. The deficits do not occur exclusively during the course of a delirium.
F. The disturbance is not better accounted for by another Axis 1 disorder.

Source: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington DC: American Psychiatric Association; 1994. p. 142–143. Reprinted with permission.

looked or attributed to other problems. The disease usually follows a fairly consistent pattern. Initial memory loss is mainly for recent events and includes the inability to retain new information. Various language problems and mood and personality changes may accompany the early stages of disease. In the intermediate stage of the illness, memory problems progress to include remote events, and physical signs begin to appear such as psychomotor retardation. Patients remain ambulatory, but are at high risk for falls. During this stage, the patient will require assistance with activities of daily living including dressing, bathing, toileting, feeding, and ambulating. Severe disease is characterized by progression to a bed-bound state, urinary and fecal incontinence, and decline in speech.

Neuroimaging

The value of performing a diagnostic neuroimaging procedure in a patient whose history and physical examination is consistent with the clinical syndrome of Alzheimer's Dementia is controversial. Benson (5) described three groups of disorders in which a change in mental status may be the only presenting sign. These include space-occupying brain lesions (such as tumors and subdural hematomas), hydrocephalus, and focal brain lucencies. These conditions account for only approximately 3.5% of all dementias. The challenge in identifying these disorders without performing CT scans in patients who present with dementia has been addressed by several studies. Deitch (6) developed a set of criteria to select patients with dementia in whom the results of the CT scan would probably not affect the patients' treatment. These criteria include:

- Dementia for at least 1 month
- No head trauma in the week preceding the change in mental status
- No history of malignant tumors, cerebrovascular accident, seizures, or urinary incontinence
- No focal cerebral signs, papilledema, visual field defect, apraxia, or ataxia of gait.

In a retrospective chart review, 1 of the 100 patients studied who met these criteria was found to have a potentially treatable disorder on CT scan. This patient had severe headaches for 2 months. On the other hand, an analysis of 100 patients who presented with dementia, but who did not meet these criteria, revealed 10 patients who had potentially treatable diseases. In a subsequent study, Alexander et al. (7) tested the sensitivity of these criteria for determining the need for a CT scan in the evaluation of demented patients. Charts were reviewed retrospectively over a 4.5-year period. The patients with surgical brain lesions who presented with isolated dementia were selected and the number fulfilling Deitch's criteria (modified to include no history of headaches and to delete history of malignant tumor) were identified and enumerated. Four of 59 patients were identified who would not have had a CT scan ordered according to the modified version of Dietch's criteria. One of these cases had cognitive impairment for 3 months at the time of presentation and another had fecal but not urinary incontinence. The remaining two patients actually did have focal findings, but these were not recorded in the patient's record prior to the CT scan. On this basis, the authors support a selective approach to neuroimaging in the evaluation of patients with dementia. More recently, McDermott and Dluzen (8) reviewed outpatient records to determine the number of potentially reversible dementias identified on routine neuroimaging, the number of these patients who were treated, and their ultimate clinical outcomes. They identified 695 patients who were evaluated for dementia or memory loss. Of these, 83% had a neuroimaging procedure; only one patient had improved cognition after treatment based on the result of the neuroimaging procedure. These authors concluded that neuroimaging should not be a part of a routine work-up for all patients with dementia. A more selective approach to the use of neuroimaging procedures would more likely benefit those particular patients who exhibit rapid progression of dementia and atypical features.

Other experts in this field have also outlined criteria for neuroimaging in the work-up of dementia. Clarfield and Larson (9) recommended considering a CT scan for patients with dementia who have any of the following characteristics:

- Age younger than 70 years
- Onset less than 1 year
- Atypical presentation
- Rapid unexplained deterioration
- Unexplained focal neurological signs or symptoms
- A history of head injury
- A history of urinary incontinence and gait ataxia early in the course of illness
- Inability of either patients or families to feel reassured without a CT scan.

They emphasized the need to assure that the diagnosis of dementia is indeed correct in all patients by obtaining a thorough history, physical (including neurological) examination, and ruling out other reversible causes of cognitive dysfunction such as depression, metabolic abnormalities, drugs, and vitamin deficiencies. They concluded that a critical review of the literature does not support the need for a neuroimaging procedure in all patients in whom dementia is diagnosed. Finally, Siu (10) reviewed selected studies that used accepted criteria to diagnose dementia. He focused on the "likelihood ratio" for each test result. This ratio represents the probability of obtaining that result in patients with the specified disease divided by the probability of obtaining that result in patients without the disease. Combining these data with the pretest odds of disease, one can calculate the post test odds of disease. In particular, he reported that a CT scan could confirm the diagnosis of multi-infarct dementia when the pretest suspicion is high. He does not recommend routine neuroimaging when the pretest probability of finding an intracranial lesion is low, especially if the findings on CT scan are not likely to alter the management of the patient. However, it is important to note that the diagnosis of a vascular lesion, for example, may alert the clinician to consider initiating treatment, if indicated, and/or to attempt better control of hypertension. Although there are no specific findings on CT scan that are diagnostic (cerebral atrophy correlates better with age than with presence or degree of dementia), it may be important to exclude the presence of significant vascular lesions before committing a patient to medication specifically intended for the treatment of Alzheimer's disease.

Choosing which patients with dementia in whom to perform neuroimaging studies depends on whether establishing an alternative diagnosis to Alzheimer's disease will alter the long-term outcome. Studies by Larson et al. (11) and Katzman (12) have specifically addressed this question. Larson prospectively studied 200 elderly outpatients with a clinical diagnosis of dementia in whom CT scans of the brain were performed. The study design included a review of each patient by a dementia diagnostic consensus group including an internist, psychiatrist, psychologist, neurologist-neuropathologist and a nurse coordinator. Each patient had a comprehensive medical evaluation, psychiatric evaluation, neuropsychological assessment, and a CT scan. In this study, no illnesses that led to treatment changes were detected by CT scanning. Katzman reviewed autopsies of those individuals who had met the accepted criteria for a clinical diagnosis of probable Alzheimer's disease and found that the diagnosis was confirmed in about 90% of autopsied subjects. For this review, accepted criteria for a clinical diagnosis were those established by a Task Force of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease Related Disorders Association. These criteria are insidious onset, progressive course, and cognitive deficits in two or more areas of cognition, including memory, and an alert and aware mental state (13). Nonetheless, Katzman suggested that although diagnosing a structural lesion or a stroke may not lead to clinical improvement or increased active life expectancy, a CT scan is warranted in the work-up of dementia to find those patients for whom treatment can be beneficial. His paper did not address issues related to the cost of the dementia work-up.

Once a diagnosis of Alzheimer's disease has been established in a patient, it is crucial to remember that superimposed treatable delirium and depression, common complications in patients with chronic dementia, are often misdiagnosed as worsening dementia. The diagnosis of delirium is based on a disturbance of consciousness with reduced ability to focus, sustain, or shift attention. A delirium develops over hours to days, tends to have a fluctuating course and can be attributed to a medical condition (14). Differentiating dementia from depression is often more difficult. One clue is that a patient with depression will make a poor effort on testing (15). When asked, for example, what is the date, a depressed patient will respond "I don't know" compared with a patient with dementia who will most often make something up. Diagnosis and treatment of both delirium and depression in the setting of dementia is often beneficial and rewarding.

In summary, I recommend that patients who present with dementia be evaluated as follows:

- Patients should be given a comprehensive medical and neurological examination, including a review of all over-the-counter and prescribed medications.
- Laboratory tests, which include a complete blood count, folate, B12 levels, thyrotropin, chemistry profile, and VDRL, should be conducted. In clinical practice, abnormalities in these profiles are often detected and should be addressed. For example, vitamin B12 deficiency does not rule out the diagnosis of Alzheimer's disease, but treatment of the B12 deficiency may improve overall mental status in response to its correction.
- Screening for depression should be performed. This can be done at every visit by asking the simple question, "Do you often feel sad or depressed?" (16).
- A neuroimaging procedure should be done for any patient younger than 70 years of age and for those who have an atypical presentation for the diagnosis of Alzheimer's disease. Typical Alzheimer's disease has an insidious onset with a progressive course of cognitive and functional decline. Extreme old age should not be considered a contraindication to a CT scan when the clinical picture suggests another condition.

A new medication, donepezil, recently has become available to treat Alzheimer's disease (17). However, one must feel comfortable with that diagnosis before committing the patient to a course of this medication. In clinical practice, this may now translate into performing more neuroimaging procedures than most studies reviewed to date have recommended. For those patients already moderately to severely demented at the time of initial presentation, the best treatment options remain those supportive measures which maximize function. The result of a neuroimaging procedure in this setting is not likely to change the outcome and is therefore unwarranted as a routine procedure.

References

1. Fleming KC, Adams AC, Petersen RC. Dementia: Diagnosis and evaluation. Mayo Clin Proc 1995; 70:1093–1107.
2. Aevarsson O, Skoog I. A population-based study on the incidence of dementia disorders between 85 and 88 years of age. J Am Geriatr Soc 1996; 44:1455–1460.
3. Koblenzer J. Clinical evaluation of dementia. Mt Sinai J Med 1993; 60:532–538.
4. Corey-Bloom J, Wiederholt WC, Edelstein S, et al. Cognitive and functional status of the oldest old. J Am Geriatr Soc 1996; 44:671–674.
5. Benson DF. Neuroimaging and dementia. Neurol Clin. 1986; 4:341–353.
6. Deitch JT. Computerized tomographic scanning in cases of dementia. West J Med 1983; 138:835–837.
7. Alexander EM, Wagner EH, Buchner DM, et al. Do surgical brain lesions present as isolated dementia? A population-based study. J Am Geriatr Soc 1995; 43:138–143.
8. McDermott JL, Dluzen DE. The value of routine neuroimaging in the evaluation of dementia in the elderly. Clin Geriatr Med 1997; 5:72–80.
9. Clarfield AM, Larson EB. Should a major imaging procedure (CT or MRI) be required in the workup of dementia? An opposing view. J Fam Pract 1990; 31:405–410.
10. Siu AL. Screening for dementia and investigating its causes. Ann Intern Med 1991; 115:122–132.
11. Larson EB, Reifler BV, Sumi SM, et al. Diagnostic tests in the evaluation of dementia. A prospective study of 200 elderly outpatients. Arch Intern Med 1986; 146:1917–1922.
12. Katzman R. Should a major imaging procedure (CT or MRI) be required in the workup of dementia? An affirmative view. J Fam Pract 1990; 31:401–405.
13. McKann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's Disease: Reprint of the NINCDS-ADRDA Work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34:939–944.
14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th revised ed. Washington DC: American Psychiatric Association; 1994. p. 129.
15. Geldmacher DS, Whitehouse PJ. Evaluation of dementia. N Engl J Med. 1996; 335:330–335.
16. Mahoney J, Drinka T, Abler R, et al. Screening for depression: single question versus GDS. J Am Geriatr Soc 1994; 42:1006–1008.
17. Rogers S, Friedhoff L, and the Donepezil Study Group. The efficacy and safety of Donepezil in patients with Alzheimer's Disease: Results of a US multicentre, randomized, double-blind, placebo-controlled trial. Dementia 1996; 7:293–303.

Antiphospholipid Antibody Syndrome:

An Acquired Cause of Venous and Arterial Hypercoagulability

Michelle Petri, M.D., M.P.H.

Abstract

Antiphospholipid antibody syndrome is a major acquired cause of both venous and arterial hypercoagulability. Recent advances in the understanding of antiphospholipid antibodies, their detection, clinical presentations, and management are reviewed. **Key Words:** antiphospholipid antibody, lupus anticoagulant, anticardiolipin, hypercoagulability

THE ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS) is one of the most common acquired causes of hypercoagulability in the general population (Table 1). It is associated with hypercoagulability in both veins and arteries and is of special concern in patients with systemic lupus erythematosus (SLE), who constitute about 50% of patients who present with APS. Antiphospholipid antibodies have been recognized for many years, but their clinical significance has only been recognized for the past decade. Both clinical and basic science research in this area have increased understanding of the pathogenesis and clinical importance of these autoantibodies.

Case Reports

Patient 1: Older Man with Multiple Strokes

A 63-year-old Caucasian man, with a history of hypertension and peptic ulcer disease, presented with a history of multiple strokes. Despite the use of warfarin and low-dose aspirin, he continued to have transient ischemic attacks. His physical examination was remarkable for livedo reticularis, a fine purple lacklike pattern on the extremities, and for mild dementia. His primary physician had obtained an anticardiolipin antibody assay, which was negative.

Patient 2: Individual with Recurrent Venous Thrombosis

A 47-year-old Caucasian man had a deep venous thrombosis several years previously, treated with warfarin. He presented with a pulmonary embolus after an airplane trip. Immobility is a known trigger of hypercoagulability.

Patient 3: A Young Athlete Dies Suddenly of Myocardial Infarction

A 28-year-old male Caucasian figure skater, with a family history of cardiac disease, died suddenly of a myocardial infarction.

Definition and Classification

Antiphospholipid antibodies comprise a family of autoantibodies directed against complexes of negatively charged phospholipids and plasma protein cofactors (1) (Table 2). There are several antiphospholipid antibodies for which clinical assays are available. The first antiphospholipid an-

---

Dr. Petri was supported by the National Institutes of Health FIRST award HL4708001. The Hopkins Lupus Cohort was supported by the Outpatient Clinical Research Center RR00722.

Address correspondence to Michelle Petri, M.D., M.P.H., Division of Rheumatology, Johns Hopkins University School of Medicine, 1830 E. Monument St., Suite 7500, Baltimore, MD 21205.

TABLE 1
Hypercoagulable States

- Acquired (secondary) causes of hypercoagulability
  - APS
  - Pregnancy
  - Oral contraceptives
  - Nephrotic syndrome
  - Hyperlipidemia
  - Diabetes mellitus
  - Postoperative states
  - Vasculitis
  - Obesity
  - Malignancy
- Genetic (primary) causes of hypercoagulability
  - Factor V Leiden (resistance to activated protein C)
  - Antithrombin III deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Fibrinolytic disorders
  - Homocystinuria
  - Platelet polymorphisms

TABLE 2
Antiphospholipid Antibodies Associated with Hypercoagulability

- Lupus anticoagulant
  - Identified by prolongation of *in vitro* clotting assays
  - Directed against β_2-glycoprotein I, prothrombin, and other plasma proteins
- Anticardiolipin
  - Identified by solid-phase ELISA assays
  - Directed against β_2-glycoprotein I, with or without negatively charged phospholipid

tibody recognized was the false-positive test for syphilis. This test still has clinical importance, because about 20% of young women with a false-positive test for syphilis will go on to develop a connective tissue disease, usually lupus, later in life (2). However, the false-positive test for syphilis is not closely associated with the clinical manifestations of APS.

The lupus anticoagulant was the second antiphospholipid antibody discovered but the first to have clinical importance as a marker of a hypercoagulable state. However, when first identified, its importance as a hypercoagulable marker was not recognized (3). Because it prolonged clotting times *in vitro,* and because many of the patients who acquired this antibody had SLE, it was given the name lupus anticoagulant. Although more than half of the patients with lupus anticoagulant do not have lupus and the lupus anticoagulant is a procoagulant *in vivo,* the double misnomer remains. The lupus anticoagulant is measured by clotting assays and therefore requires plasma. International committees have developed a three-step program to identify lupus anticoagulants in a standardized manner. The first step is a sensitive screening assay. Multiple screening assays may need to be done, because the lupus anticoagulant is a heterogeneous autoantibody and no one assay has been developed that can identify 100% of these autoantibodies. The second step is to determine the effect of mixing both normal and sample plasmas. Unlike factor deficiencies, which will correct with a 1:1 mixture, lupus anticoagulants usually will not correct. However, some lupus anticoagulants do correct, and in that situation a 4:1 mixture with normal plasma will allow their identification. The third step in the confirmation of a lupus anticoagulant is to demonstrate that it depends on phospholipid. This can be done by a phospholipid neutralization procedure (4). Patients with APS may make one antiphospholipid antibody, such as the lupus anticoagulant, and not another. Thus, the first patient should have had lupus anticoagulant assays performed before ruling out the possibility of APS.

The third antiphospholipid antibody, anticardiolipin antibody, also has clinical importance. Unlike the lupus anticoagulant, the anticardiolipin antibody is identified by solid-phase assays and therefore can be done on stored sera. Anticardiolipin antibody assays are often isotype specific, but of the different isotypes, the IgG isotype is most closely associated with the clinical presentations of APS.

Other antiphospholipid antibodies exist, but many of them do not yet have sufficient clinical importance to warrant their use in general clinical practice. It has been recognized recently that anticardiolipin antibodies are predominantly directed against the plasma protein called β_2-glycoprotein I (5). Many of the solid-phase antiphospholipid antibodies do not even require the negatively charged phospholipid for binding (6). In the future, assays for autoantibodies directed against β_2-glycoprotein I alone may have a place in clinical practice (7).

Clinical criteria have been developed for the diagnosis of APS (Table 3). As with most diagnostic criteria, they are used to categorize patients

TABLE 3
Classification Criteria for APS

- Presence of the lupus anticoagulant and/or moderate- or high-titer anticardiolipin IgM/IgG
- Presence of one or more major criteria
  - Venous thrombosis
  - Arterial thrombosis
  - Pregnancy loss (recurrent first trimester losses or late pregnancy loss)
  - Thrombocytopenia

for inclusion in research studies and may not be quite as useful in clinical practice. The four clinical criteria for APS are venous thrombosis, arterial thrombosis, recurrent pregnancy loss, and/or thrombocytopenia. One of these four criteria must be present, along with the presence of either the lupus anticoagulant or moderate- to high-titer IgM or IgG anticardiolipin to classify a patient with APS (8). There are several problems with the clinical criteria as they are devised currently. For example, there are several presentations of APS that appear to be quite specific, and yet are not currently covered by the criteria. For example, certain neurologic manifestations, such as chorea and transverse myelopathy, are not included in the current criteria. The criterion for recurrent pregnancy loss is also quite problematic. Late losses in the second or third trimester are most specific for APS. Recurrent first trimester idiopathic abortion can also occur in patients with APS, but only a minority of women with recurrent habitual abortion have antiphospholipid antibodies (9). Consequently, the criterion for pregnancy loss might be better stated as recurrent pregnancy loss in the first trimester or late pregnancy loss not due to other causes.

About 50% of patients with APS have systemic lupus erythematosus or a lupus-like syndrome. Other connective tissue diseases, malignancy, and some drugs can also be associated with APS. Most antiphospholipid antibodies induced by infection are not associated with a hypercoagulable state. This appears to be due to the fact that they are directed against phospholipid, without the requirement for the plasma protein cofactor. An example of these infection-induced antiphospholipid antibodies (which are not usually associated with a hypercoagulable state) would be the antiphospholipid antibodies that are usually found in patients with HIV infection or AIDS (10).

Patients who have APS due to lupus are categorized as having the secondary form of APS (11). Patients who do not have any known connective tissue disease are labeled as having the primary form of APS (12).

Frequency of APS

Antiphospholipid antibodies are extremely common in the general population. Many studies that have used lupus anticoagulant, anticardiolipin antibody assays, or both, have found that 1 to 5% of the general population have antiphospholipid antibodies (13). Antiphospholipid antibodies may increase with age, although studies on this issue have disagreed. In one study as many as 50% of patients older than 80 years of age had antiphospholipid antibodies (14). Because the *a priori* hypothesis of the frequency of antiphospholipid antibody positivity would be very high in the elderly, it is not clear how helpful these assays would be diagnostically in an elderly patient who had a stroke. However, the first patient, although elderly, had another clue that would have mandated a search for APS. He had livedo reticularis, the most common cutaneous manifestation of APS.

Antiphospholipid antibodies are much more common in patients with SLE than they are in the general population. We have found that 50% of patients with SLE, when followed up longitudinally, have low to moderate titers of either lupus anticoagulant or anticardiolipin, or both, on one or more occasions.

Although antiphospholipid antibodies are frequently found in patients with SLE followed up longitudinally, the exact prevalence of APS in patients with SLE is uncertain. The quality of the assays, the number of times the assays are repeated, and referral bias to academic centers have led to differing estimates. Hughes (15) has quoted a frequency of 35% for APS in SLE. McNeil et al. (16) concluded that the frequency of thrombosis was 42% in antiphospholipid antibody-positive patients with SLE and 31% in all patients with antiphospholipid antibodies. In our experience, the frequency of thrombosis and the frequency of APS in SLE is less. This may be because the cohort in our study is 50% African-American in whom antiphospholipid antibodies are found less frequently.

Because more than half of the patients with APS do not have SLE, it is very important to ascertain the frequency of these clinical presentations in the non-SLE population. In one study of 100 patients who had verified venous thrombosis, 24% had anticardiolipin and 4% had the lupus anticoagulant (17). There have been many more studies of the frequency of antiphospholipid antibodies in patients with stroke. The frequency of antiphospholipid antibodies in unselected patients with thrombotic stroke has ranged from 6% to 29%. Several studies have included control groups and have found that the frequency of antiphospholipid antibodies in patients with stroke is significantly higher than in control subjects. The association of antiphospholipid antibodies with stroke is much stronger in patients younger than 50 years of age (18). In studies using anticardioloipin assays in young patients with stroke, the frequency of positive assays has ranged from

18% to 46%. In studies that have used lupus anticoagulant assays, the frequency has been less, in the range of 2% to 4%. The frequency of APS in non-lupus patients with recurrent fetal loss has varied widely, but an estimate of 12% to 15% is reasonable (13).

Assays for Antiphospholipid Antibodies

The lupus anticoagulant appears to have several targets, including β_2-glycoprotein I and prothrombin. β_2-Glycoprotein I is a naturally occurring anticoagulant. Among the screening assays with good sensitivity for lupus anticoagulants are the modified Russell viper venom time, the kaolin clotting time, and the sensitive partial thromboplastin time. It is important to use a battery of screening assays, because no one assay will be capable of detecting all patients that have the lupus anticoagulant.

Anticardiolipin antibody assays have been refined over time to improve their sensitivity and their specificity. Anticardiolipin assays are currently performed using enzyme-linked immunosorbent assay (ELISA) technology. Typically IgG, IgM, and IgA isotypes are determined, although only the IgG and IgM isotypes have been clearly shown to have clinical significance. In the future, assays to detect antibodies to β_2-glycoprotein I alone may enter clinical practice, although currently they are predominantly used in the research arena.

Pathogenesis and Pathology

When biopsies of skin and other lesions are performed in patients with APS, the pathology is a bland, noninflammatory thrombosis (19). This is obviously very different from SLE in which evidence of vasculitis and fibrinoid necrosis is found.

The pathogenesis of APS remains obscure. In cross-sectional studies of patients who have had thrombotic events, multiple perturbations in coagulation control are typically found. This might indicate that the different antiphospholipid antibodies have multiple mechanisms of action or that antiphospholipid antibodies alone are not sufficient to cause a hypercoagulable state, requiring a “second hit.” Some patients with APS have been shown to have an imbalance of thromboxane and prostacyclin (20). Antiphospholipid antibodies also bind to activated platelets (21). An additional potential mechanism is the effect of these antiphospholipid antibodies on the Protein C/Protein S/thrombomodulin system (1). In our work, patients with APS were not found to have an increase in the Factor V Leiden mutation, a genetic mutation that leads to resistance to activated Protein C.

Clinical Features

Thrombosis

The most common presentation of APS is venous thrombosis, typically recurrent venous thrombosis. The usual location is a deep venous thrombosis of the lower extremities. Patient 2, with recurrent venous thrombosis, should definitely be screened for APS as well as for other causes of venous hypercoagulability, such as Factor V Leiden. Arterial thrombosis often involves the brain and presents with transient ischemic attacks or thrombotic stroke. Some of the strokes are embolic in nature because of vegetations on the mitral or aortic valve. Thromboses, however, can be widespread and involve retinal arteries, subclavian arteries, and coronary arteries, and they result in digital gangrene and myocardial infarction. Patient 3 might well have APS, but his presentation would not be common. A search for other causes of arterial hypercoagulability, including homocysteinemia and platelet polymorphisms (22), would be indicated.

Fetal Loss

The specific type of pregnancy loss associated with APS is late pregnancy loss. In our studies of pregnancy in SLE, these losses cluster around the 20th week of gestation. It is not clear from pathologic studies of the placenta that these losses are caused by placental thrombosis alone. It is possible that the problem is on the uterine side of the uteroplacental unit. The patients with APS who have recurrent first trimester idiopathic habitual abortion are likely to have a different pathogenetic mechanism.

Other Clinical Features

Other clinical features of APS are not clearly thrombotic in nature (Table 4). In the United States, chorea is just as commonly found with APS as it is with rheumatic fever (23). The chorea of APS can respond rapidly to corticosteroid therapy, often without any infarcts found in the basal ganglia. Transverse myelopathy, too, can be associated with APS and may respond to large doses of intravenous corticosteroids (24).

An unusual cardiac presentation is valvular disease, usually involving mitral or aortic valves. Occasionally, the valvular destruction warrants valve replacement. A recent focus of research has

TABLE 4
Other Clinical Features of APS

Neurologic	Stroke, transient ischemic attack, chorea, transverse myelopathy, multi-infarct dementia, epilepsy, complicated migraine, encephalopathy, cerebral venous sinus thrombosis, anterior spinal artery syndrome
Cardiac	Myocardial infarction, angina, cardiac vasculopathy, valvular disease, intracardiac thrombosis
Dermatologic	Livedo reticularis, superficial thrombophlebitis, leg ulcers, splinter hemorrhages
Endocrinologic	Adrenal hemorrhage
Pulmonary	Pulmonary emboli, pulmonary hypertension, pulmonary hemorrhage, fibrosing alveolitis
Renal	Renal artery thrombosis, renal vein thrombosis, hypertension, glomerular capillary thrombosis
Gastrointestinal	Budd-Chiari syndrome, hepatic infarction, splenic infarction

TABLE 5
Management of APS

- Prophylactic therapy
  - Reduce or eliminate other risk factors for hypercoagulability
  - Consider hydroxychloroquine in patients with SLE
- Therapy post thrombosis
  - High-intensity warfarin (unless the patient is profoundly thrombocytopenic)
- Therapy for pregnancy loss
  - Heparin and low-dose aspirin

been the possible association of antiphospholipid antibodies with atherosclerosis. Antiphospholipid antibodies do recognize oxidized low-density lipoprotein (LDL) (25). In recent work presented in abstract form, Matsuura et al. (26) found that β_2-glycoprotein I in the absence of antiphospholipid antibodies may actually protect against atherosclerosis by inhibiting the uptake of oxidized LDL. In the presence of antiphospholipid antibodies, β_2-glycoprotein apparently increases the uptake of oxidized LDL, which may explain the association with atherosclerosis.

Other important clinical manifestations of APS include its many dermatologic manifestations, such as livedo reticularis, superficial thrombophlebitis, splinter hemorrhages, and leg ulcers (27). An unusual complication of APS is adrenal hemorrhage.

Treatment

Prophylactic therapy (Table 5) which would prevent or reduce thrombotic events in patients with SLE would be worthwhile. Low-dose aspirin is most frequently prescribed. However, in the Physician's Health Study, in which half of the male physicians were randomly selected to receive aspirin, a protective effect of aspirin was not found in those individuals with anticardiolipin antibody (28). In our prospective study of patients with SLE, the use of nonsteroidal anti-inflammatory drugs was not found to protect against thrombosis in those patients who were antiphospholipid antibody positive. We found that hydroxychloroquine protects against future thrombosis in patients with SLE (29). It is extremely important to eliminate other risk factors for thrombosis that these patients may have, such as oral contraceptives and smoking, and to treat aggressively other risk factors such as hypertension and hyperlipidemia.

The treatment of patients who have already had a thrombotic event is based on three published series of patients (30–32). Warfarin is recommended in a dosage schedule to maintain an international normalized ratio (INR) between 3 and 4. Obviously, high-intensity warfarin should not be given to patients who are profoundly thrombocytopenic. In our view, patients should not be started on warfarin unless the platelet count can be maintained at more than 50,000/mm^3. Some authorities (33) believe that high-intensity warfarin may be unnecessarily aggressive for patients who have had venous thrombotic events alone. However, we have had several patients who initially presented with venous thrombotic events who later had arterial thrombotic events.

The pregnant patient with APS is treated predominantly with subcutaneous heparin and aspirin. Earlier regimens of prednisone and aspirin may have been equally effective in terms of fetal survival, but were associated with greater morbidity, including pre-eclampsia, preterm birth, diabetes, osteoporosis, and cataracts (34). Low molecular weight heparin seems to work well in case series and has potential advantage over conventional heparin because only one daily injection is required. Moreover, its use leads to less osteoporosis and heparin-induced thrombocytopenia. Thus, the future treatment of the obstetrical patient with APS may shift to low molecular weight heparin and aspirin. Women who fail these regimens may be candidates for intravenous γ-globulin.

Conclusion

The antiphospholipid antibody syndrome has been well described clinically, but its pathogenesis remains elusive. The current requirement for adequate long-term warfarin treatment after a thrombotic event caused by APS certainly will not be the final word. The goal of research will be to effect the safe and long-term reduction or elimination of antiphospholipid antibodies to prevent both primary and secondary thromboses and pregnancy loss.

References

1. Oosting JD, Derksen RHWM, Bobbink IWG, et al. Antiphospholipid antibodies directed against a combination of phospholipids with prothrombin, protein C or protein S: An explanation for their pathogenic mechanism? Blood 1993; 81:2618–2625.
2. Moore JE, Mohr CF. Biologically false positive serologic tests for syphilis. JAMA 1952; 150:467–473.
3. Conley CL, Hartmann RC. A hemorrhagic disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus. J Clin Invest 1952; 31:621–622.
4. Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. Thromb Haemostasis 1995; 74:1185–1190.
5. McNeil HP, Simpson RJ, Chesterman CN, Krilis SA. Antiphospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor: β_2-glycoprotein I (apolipoprotein H). Proc Natl Acad Sci USA 1990; 87:4120–4124.
6. Cabral AR, Cabiedes J, Alarcón-Segovia D. Antibodies to phospholipid-free β_2-glycoprotein-I in patients with primary antiphospholipid syndrome. J Rheumatol 1995; 22:1894–1898.
7. Viard J-P, Amoura Z, Bach J-F. Association of anti-β_2-glycoprotein I antibodies with lupus-type circulating anticoagulant and thrombosis in systemic lupus erythematosus. Am J Med 1992; 93:181–186.
8. Asherson RA, Cervera R. Anticardiolipin antibodies, chronic biologic false positive tests for syphilis and other antiphospholipid antibodies. In: Wallace DJ, Hahn BH, editors. Dubois' Lupus Erythematosus. 4th ed. Philadelphia: Lea & Febiger; 1993.
9. Petri M, Golbus M, Anderson R, et al. Antinuclear antibodies, lupus anticoagulant, and anticardiolipin antibody in women with idiopathic habitual abortion. A controlled, prospective study of forty-four women. Arthritis Rheum 1987; 30:601–606.
10. Hunt JE, McNeil HP, Morgan GJ, et al. A phospholipid-beta 2-glycoprotein I complex is an antigen for anticardiolipin antibodies occurring in autoimmune disease but not with infection. Lupus 1992; 1:75–81.
11. Alarcón-Segovia D, Delezé M, Oria CV, et al. Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus: A prospective analysis of 500 consecutive patients. Medicine 1989; 68:353–374.
12. Alarcón-Segovia D, Sánchez-Guerrero J. Primary antiphospholipid syndrome. J Rheumatol 1989; 16:482–488.
13. Petri M. Epidemiology of the antiphospholipid syndrome. In: Asherson RA, Cervera R, Piette J-C, Shoenfeld Y, editors. The antiphospholipid syndrome. CRC Press: Boca Raton; 1996. pp. 13–28.
14. Manoussakis MN, Tzioufas AG, Silis MP, et al. High prevalence of anti-cardiolipin and other autoantibodies in a healthy elderly population. Clin Exp Immunol 1987; 69:557–565.
15. Hughes GRV. The antiphospholipid syndrome: Ten years on. Lancet 1993; 342:341–344.
16. McNeil HP, Hunt JE, Krilis SA. Antiphospholipid antibodies: New insights into their specificity and clinical importance. Scand J Immunol 1992; 36:647–652.
17. Bick RL, Jakway J, Baker Jr. WF. Deep vein thrombosis: prevalence of etiologic factors and results of management in 100 consecutive patients. Semin Thromb Hemostasis 1992; 18:267–274.
18. Brey RL, Hart RG, Sherman DG, Tegeler CH. Antiphospholipid antibodies and cerebral ischemia in young people. Neurology 1990; 40:1190–1196.
19. Alegre VA, Winkelman RK. Histopathologic and immunofluorescence study of skin lesions associated with circulating lupus anti-coagulant. J Am Acad Dermatol 1988; 19:117–124.
20. Carreras LO, Vermylen J, Spitz B, van Assche A. "Lupus" anticoagulant and inhibition of prostacyclin formation in patients with repeated abortion, intrauterine growth retardation and intrauterine death. Br J Obstet Gynecol 1981; 88:890–894.
21. Martinuzzo ME, Maclouf J, Carreras LO, Lévy Toledano S. Antiphospholipid antibodies enhance thrombin-induced platelet activation and thromboxane formation. Thromb Haemost 1993; 70:667–671.
22. Goldschmidt-Clermont PJ, Shear WS, Schwartzberg J, et al. Clues to the death of an Olympic champion. Lancet 1996; 347:1833.
23. Asherson RA, Derksen RHWM, Harris EN, et al. Chorea in systemic lupus erythematosus and "Lupus-Like" disease: Association with antiphospholipid antibodies. Semin Arthritis Rheum 1987; 16:253–259.
24. Chang R, Quismorio Jr. P. Transverse myelopathy in systemic lupus erythematosus (SLE) [abstract]. Arthritis Rheum 1990; 33:S102.
25. Vaarala O, Alfthan G, Jauhiainen M, et al. Cross reaction between antibodies to oxidized low-density lipoprotein and to cardiolipin in systemic lupus erythematosus. Lancet 1993; 341:923–925.
26. Matsuura E, Hasunuma Y, Makita Z, et al. Oxidatively modified LDL as a target for β_2-glycoprotein I antibodies [Abstract]. Lupus 1996; 5:517.
27. Grob JJ, Bonerandi JJ. Cutaneous manifestations associated with the presence of the lupus anticoagulant. J Am Acad Dermatol 1986; 15:211–219.
28. Ginsburg KS, Liang MH, Newcomer L, et al. Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. Ann Intern Med 1992; 117:997–1002.
29. Petri M. Thrombosis and systemic lupus erythematosus: The Hopkins Lupus Cohort perspective. Scand J Rheumatol 1996; 25:191–193.
30. Khamashta MA, Cuadrado MJ, Mujic F, et al. The

management of thrombosis in the antiphospholipid antibody syndrome. N Engl J Med 1995; 332:993–997.

31. Rosove MH, Brewer PMC. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. Ann Intern Med 1992; 117:303–308.
32. Derksen RHWM, de Groot PG, Kater L, Nieuwenhuis HK. Patients with antiphospholipid antibodies and venous thrombosis should receive long term anticoagulant treatment. Ann Rheum Dis 1993; 52:689–692.
33. McCrae KR. Antiphospholipid antibody associated thrombosis: A consensus for treatment? Lupus 1996; 5:560–570.
34. Cowchock FS, Reece EA, Balaban D, et al. Repeated fetal losses associated with antiphospholipid antibodies: A collaborative randomized trial comparing prednisone with low-dose heparin treatment. Am J Obstet Gynecol 1992; 166:1318–1323.

Acute Gouty Sacroiliitis:

A Case Report and Review of the Literature

Bahar Bastani, M.D.,[1] Ravi Vemuri, M.D.,[2] and Mark Gennis, M.D.[2]

Abstract

A 45-year-old black woman with an acute attack of severe unilateral sacroiliitis, negative microbiologic studies, is presented. An open biopsy specimen of the sacroiliac joint revealed evidence of tophaceous gout. The unique features of the case, differential diagnosis, and pertinent literature on gouty sacroiliitis are reviewed. Acute gouty sacroiliitis, although it is rare, does occur and should be included in the differential diagnosis of unilateral sacroiliitis in patients with a long-standing history of gout. **Key Words:** gout, sacroiliitis, sacroiliac joint, arthritis

It is well known that both acute and chronic tophaceous gout primarily affect the appendicular skeleton and that the axial skeleton is generally spared. Two studies (1, 2) reported that 7.5% and 17% of the patients with chronic gout were found to have radiologic evidence of tophaceous involvement of the sacroiliac joints (SIJs) on anteroposterior pelvic roentgenogram. However, acute sacroiliitis was clinically present in only 3 of 34 patients who had the classic radiologic findings. Our patient represents another example of acute sacroiliitis caused by gout. The lack of peripheral tophi makes it unique.

Case Presentation

A 45-year-old black woman was admitted with an acute onset of severe aching pain in the left buttock, radiating to her left thigh posteriorly. Pain had started spontaneously upon awakening on the day of admission. She denied falling or sustaining any trauma to the region. She had a history of chronic midline low-back pain which was unchanged on this admission. She had no history of fever, chills, morning stiffness, gastrointestinal symptoms, or intravenous drug use. Her past medical history was significant for electromyographic evidence of L5-S1 radiculopathy on the left side, an old cerebrovascular accident (CVA) with residual left upper extremity weakness, migraine headaches, hypertension, obesity, peptic ulcer disease, hysterectomy, and osteoarthritis. Six years earlier she had been diagnosed as having gout, with eight attacks in her first metatarsophalangel and ankle joints up to the present illness. She denied consumption of alcohol or binge eating. Of 12 siblings, only one brother and one sister were known to have gout. Her medications on admission included indapamide 2.5 mg/day and colchicine 0.6 mg/day.

Physical examination revealed a markedly obese woman with weight 117 kg; height, 161 cm; temperature, 100°F; blood pressure, 180/100 mm Hg; pulse rate, 100 beats/min. She was in marked distress and could not move without experiencing severe pain in the left buttock region. The left SIJ was severely tender upon direct pressure without increase in warmth or redness. She was unable to stand because of severe pain. She had no evidence of any other joint disease, tophi, or subcutaneous nodules. She had a slight weakness in the left

---

From the Departments of Internal Medicine, [1]St. Louis University Health Sciences Center, St. Louis, MO, and [2]Sinai Samaritan Medical Center, Milwaukee, Wisconsin. Address correspondence to Bahar Bastani, M.D., Associate Professor of Medicine, Department of Internal Medicine, Division of Nephrology, St. Louis University Health Sciences Center, 3635 Vista Ave., 9th Floor North, St. Louis, MO 63110.

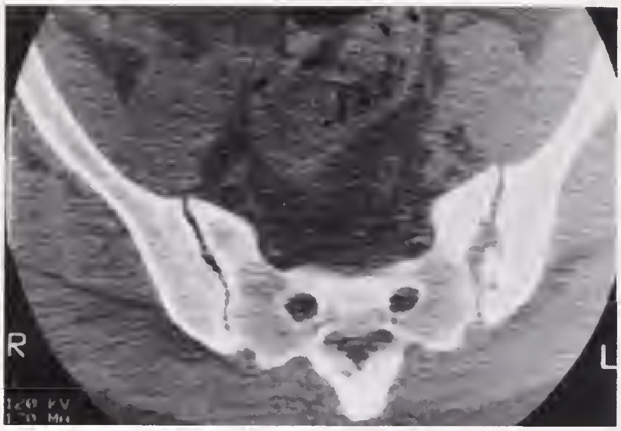


Fig. 1. CT scan of the pelvis reveals significant erosive destruction of the subchondral bone in the midportion of the left sacroiliac joint, more prominent in the iliac aspect, with sclerotic changes more prominent in the sacral aspect of the joint.

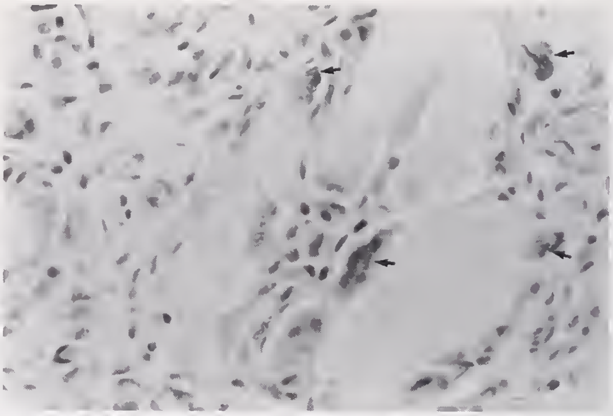


Fig. 2. A portion of a gouty tophus present in articular cartilage from sacroiliac biopsy. Urate crystals, originally present, dissolved during processing leaving only a proteinaceous matrix preserved in the center. This is surrounded by granulation tissue with numerous multinucleated giant cells (arrow).

extremities, residual from her old CVA. Sphincter tone was normal as were deep tendon reflexes.

Her laboratory data included: white blood cell (WBC) count, 11.6 × 10^9 cells/L (11,600/mm^3) with a normal differential count; erythrocyte sedimentation rate (ESR), 120 mm/hr (Westergren); and uric acid, 0.554 mmol/L (9.4 mg/dL). Antinuclear antibody and rheumatoid arthritis titers were normal. A PPD skin test was nonreactive with a positive reaction to mumps antigen applied simultaneously.

Hospital Course

The midline low-back pain gradually improved with bed rest and intramuscular injections of meperidine and hydroxyzine. However, the left SIJ pain and tenderness worsened and became more focal. She had a spike of temperature, up to 101.8°F orally, and 5 days of low-grade fever after which she became afebrile. The WBC count gradually normalized without antibiotic treatment. Anteroposterior roentgenogram of the pelvis did not reveal any abnormality. Bone scintigraphy showed increased uptake in the left SIJ. The computerized tomography (CT) scan of the pelvis revealed normal right SIJ, but significant erosive destruction of the subchondral bone in the midportion of the left SIJ (Fig. 1). A needle aspiration of the left SIJ, under fluoroscopy, yielded only a few milliliters of bloody fluid with negative Gram stain, culture, mycobacterial and fungal smears and cultures. An open biopsy of the left SIJ was obtained. Gram stain, acid fast stain, cultures for aerobic and anaerobic bacteria, as well as cultures for mycobacteria and fungi were all negative. A portion of a gouty tophus was seen and is illustrated in Fig. 2. Before the biopsy was attempted, she had developed severe pain with some swelling in both midfoot regions as well as in the bases of her big toes bilaterally. After the biopsy was done, oral colchicine was increased to 0.6 mg three times daily and indomethacin was started at 75 mg daily, which markedly reduced the pain in her left buttock and both feet within 24 hours. She did not tolerate higher doses of colchicine because of its gastrointestinal side effects. At the time of discharge, she was able to ambulate with a walker. During the hospital course, indapamide was stopped and enalapril was started for better blood pressure control. At the time of discharge, she had an ESR of 40 mm/hr and uric acid level of 0.33 mmol/L (5.6 mg/dL).

Discussion

Sacroiliitis may be bilateral (symmetric or asymmetric) or unilateral. The pattern of involvement of this joint is highly suggestive of the underlying disease process. Bilateral symmetrical sacroiliitis is a constant feature of ankylosing spondylitis to the point that, in its absence, the diagnosis should be reevaluated (3, 4). Rheumatoid arthritis also involves both SIJs symmetrically. However, it is typically mild and appears late in the course of the illness (6). Asymmetric bilateral sacroiliitis is seen in Reiter's disease (5), psoriatic arthritis (6), inflammatory bowel disease (7), and osteoarthritis. An occasional patient with any of these conditions may have unilateral joint involvement. The most common causes of unilateral sacroiliitis are infection, trauma, or metastatic cancer. The infectious causes of sacroiliitis include bacterial (8, 9), mycobacterial (10), and fungal (11).

In the present case, the history, physical examination, joint aspiration, and histology found in the biopsy of the joint excluded all the abovementioned etiologies. Her normal pelvic roentgenogram, despite markedly abnormal CT scan and bone scintigraphy, confirms the notion that the latter two are more sensitive. The plain films of the pelvis have been shown to be the least sensitive method of detecting sacroiliac joint diseases (12). Despite its great sensitivity, bone scintigraphy has the lowest specificity among the radiological imaging techniques available. CT scan or magnetic resonance imaging of the SIJ are the most accurate radiologic tests for revealing the joint anatomy and its abnormalities.

There are two reports on the frequency of SIJ involvement on plain anteroposterior roentgenograms of the pelvis in patients with chronic gout (1, 2). In one report (1) three patients, one with acute recurrent sacroiliac gouty arthritis and two patients with clinically inactive tophaceous involvement of the SIJ, were described. All three had punched-out cystic lesions with sclerotic rims of varying sizes in or near the articular surface. Such lesions are typical radiologic signs of gouty SIJ involvement. Two patients had postmortem documentation of monosodium urate crystals in the cystic bone lesions. In retrospect, they found the characteristic radiologic signs in the SIJs of 7 of 95 patients (7.5%) with history of chronic gouty arthritis (1). None of these patients had any clinical evidence of acute sacroiliitis.

The other study (2) included 143 patients with primary gout, 24 of whom (17%) had the characteristic radiologic features of SIJ involvement on the plain anteroposterior roentgenograms of the pelvis. The left side was more frequently involved than the right side (seven versus two patients), and when the SIJ involvement was bilateral (15 patients), it was usually more marked on the left (2). Only two patients had episodes of sacroiliac joint pain suggestive of acute gouty attacks (2). Most patients (96%) were male. The patients with SIJ involvement typically had an earlier onset of gout compared with those with no SIJ involvement (32 versus 40 years old), had a rapid course into chronicity, as well as a prolonged chronic stage (13.3 versus 8.7 years) which had resulted in large and sometimes enormous gouty tophi. Thus, in a total of 34 patients with gouty involvement of the SIJ, only three had acute attacks of sacroiliitis and only two were female (1, 2).

This patient demonstrates that chronic gout may present as an acute gouty attack involving the sacroiliac joint without any evidence of advanced gout in other joints (13, 14) or any peripheral tophi. Gouty arthritis should be considered in the differential diagnosis of acute unilateral sacroiliitis in a patient with a long history of gout, even in the absence of peripheral tophi.

Acknowledgment

The author would like to thank Ms. Laura Furdek for her secretarial assistance in the preparation of this manuscript.

References

1. Malawista SE, Seegmiller JE, Hathaway BE, Sokoloff L. Sacroiliac gout. JAMA 1965; 194(9):954–956.
2. Alarcon-Segovia D, Cetina JA, Diaz-Jouanen E. Sacroiliac joints in primary gout: Clinical and roentgenographic study of 143 patients. Am J Roentgenol 1973; 118:438–443.
3. Moll MJH, Wright V. New York clinical criteria for ankylosing spondylitis. Ann Rheum Dis 1973; 32:354–363.
4. Ankylosing spondylitis. In: Rodnan GP, Schumacher HR. Primer on the rheumatic diseases. 8th ed. Atlanta: Arthritis Foundation; 1983, p. 85–88.
5. Reiter's Syndrome. In: Rodnan GP, Schumacher HR. Primer on the rheumatic diseases. 8th ed. Atlanta: Arthritis Foundation; 1983. p. 88–91.
6. Dixon A St J, Lience E. Sacroiliac joint in adult rheumatoid arthritis and psoriatic arthropathy. Ann Rheum Dis 1961; 20:247–257.
7. Arthritis associated with chronic inflammatory disease of the intestine. In: Rodnan GP, Schumacher HR. Primer on the rheumatic diseases. 8th ed. Atlanta: Arthritis Foundation; 1983. p. 92–93.
8. Gordon G, Kabins SA. Pyogenic sacroiliitis. Am J Med 1980; 69:50–56.
9. Coy JT, Wolf CR, Brower TD, Winter WG. Pyogenic arthritis of the sacro-iliac joint, long term follow up. J Bone Joint Surg 1976; 58:845–849.
10. Pouchot J, Vinceneux P, Barge J, et al. Tuberculosis of the sacroiliac joint: Clinical features, outcome, and evaluation of closed needle biopsy in 11 consecutive cases. Am J Med 1988; 84:622–628.
11. Hoffman GS. Mycobacterial and fungal infections of bones and joints. In: Kelley WN, Harris ED, Ruddy S, Sledge CT, editors. Textbook of rheumatology. 2nd ed. Philadelphia: WB Saunders; 1985. p. 1527–1540.
12. Carrera GF. Current concepts in the evaluation of sacroiliitis. Postgrad Radiol 1983; 3:97–118.
13. Yu Tsai Fan. Some unusual features of gouty arthritis in females. Semin Arthritis Rheum 1977; 6:247–255.
14. Lally EV, Ho G, Kaplan SR. The clinical spectrum of gouty arthritis in Women. Arch Intern Med 1986; 146:2221–2225.

Extended-Interval Dosing of Aminoglycosides

MICHAEL E. BLAM, M.D., AND GLENN S. HAMMER, M.D.

Abstract

Aminoglycosides are efficacious agents. Their use has declined partly because of the development of newer, presumably less toxic agents. Research shows that aminoglycosides can be dosed differently than in the past, maintaining efficacy while reducing aminoglycoside toxicities. Aminoglycosides administered with newer agents may help overcome antibiotic bacterial resistance and thus yield safe and more effective therapy. This study focused on the efficacy and safety of the aminoglycosides extended-interval dosing regimen and was conducted by a search of the literature. Data from The Mount Sinai Hospital regarding bacterial resistance patterns were collected. A nomogram describing the administration of the extended-interval dosing regimen is provided. Extended-interval dosing of aminoglycosides is as efficacious as administering these agents every 8 hours and may result in lower rates of toxicities. Extended-interval dosing also may cost less and be easier to administer. Aminoglycosides are less susceptible to bacterial resistance than many of the newer, currently favored antibiotics. Increasing the usage of aminoglycosides is likely to be safe and beneficial in the treatment of certain bacterial infections. **Key Words:** aminoglycosides, therapeutics, gentamicin, once-daily dosing

AMINOGLYCOSIDES ARE BACTERICIDAL ANTIBIOTICS that are primarily indicated in the treatment of serious, aerobic Gram-negative infections and in combination with cell-wall active agents for the therapy of enterococcal endocarditis (1). Use of these agents has traditionally been limited by nephrotoxicity (7% in most series), ototoxicity, and a narrow toxic-therapeutic window. Extended-spectrum penicillins, third-generation cephalosporins, and quinolones have decreased the need for aminoglycosides, permitting the safer application of efficacious antimicrobial therapy. Aminoglycosides have thus become second-line agents. Resistance to these newer antibiotics, however, justifies reexamination of the aminoglycosides.

Emergence of resistance to the quinolones, extended-spectrum penicillins, and cephalosporins is well documented and occurring more frequently. Concern regarding emerging imipenem resistance is also growing. As an example, data collected at the Mount Sinai Medical Center show that resistance to the commonly used third-generation cephalosporins occurs in 20 to 35% of isolates of *Klebsiella pneumoniae,* 13 to 16% of isolates of *Pseudomonas aeruginosa,* in 41 to 44% of isolates of *Enterobacter cloacae,* and in 38 to 89% of isolates of *Acinetobacter* species.[1] Likewise, only 81% of *P. aeruginosa* and 61% of *Acinetobacter* species are sensitive to ciprofloxacin. Imipenem sensitivity is 98% for *E. cloacae,* but it is only 80% for the *Acinetobacter* species. These statistics are poorer for the extended-spectrum penicillins.[1]

The aminoglycosides, however, show improved sensitivity rates for *P. aeruginosa, E. cloacae,* and *Acinetobacter* species, and show sensitivity rates similar to the third-generation cephalosporins for *K. pneumoniae.*[1] Animal stud-

---

Address correspondence to Michael E. Blam, M.D., The Mount Sinai School of Medicine, Department of Medicine, Box 1118, One East 100th Street, New York, NY 10029-6574.

[1] Data are from unpublished records of The Mount Sinai Hospital, New York, on antibiotic resistance. Duncsak P, Boyle J. Antibiotic Susceptibility of Microorganisms Isolated. The Mount Sinai Hospital. July–October 1995.

ies further suggest that the emergence of resistance is decreased when β-lactams are used in conjunction with aminoglycosides. Even short-term (2–3 day) use of aminoglycosides as part of a combination regimen will decrease the emergence of β-lactam resistance by reducing to the greatest possible extent a large initial bacterial burden (1). For patients with significant β-lactam allergy, aminoglycosides may be the agents of choice when treating aerobic Gram-negative infections (1, 2).

Empiric aminoglycoside use is indicated for suspected infection caused by Gram-negative species, particularly when *Pseudomonas* is a concern (1). With definitive cultures, aminoglycosides coadministered with antipseudomonal penicillins are indicated as therapy against *Pseudomonas, Klebsiella, Enterobacter, Serratia, Enterococcus,* viridans streptococci, and *Staphylococcus* (methicillin-sensitive) (1). Prophylactic use of gentamicin with ampicillin (or with vancomycin for patients allergic to penicillin) is indicated for genitourinary and gastrointestinal surgeries in patients with valvular heart disease who are at risk for enteroccal bacteremic seeding (1).

Studies suggest that aminoglycoside toxicities (renal insufficiency and ototoxicity) may be reduced by using an extended-interval dosing regimen without sacrificing efficacy (2, 3, 7–10). Extended-interval dosing and serum monitoring are also simplified as compared with the traditional dosing schedule. The following discussion provides the evidence for extended-interval dosing of aminoglycosides and describes a nomogram for its use.

Theoretical Basis

The traditional dosing regimen for aminoglycosides (every 8–12 hr) is intended to maintain the serum concentrations above the minimal inhibitory concentration (MIC) of the infecting bacterium throughout most of the dosing interval.[2] This design assumes that bactericidal activity occurs once the MIC is reached and that the regrowth of organisms during the interval is maximally suppressed as long as the MIC is maintained. It also assumes that high peak serum concentrations correlate with toxicity, as for the β-lactams. Studies indicate, however, that aminoglycosides exhibit concentration-dependent killing and postantibiotic effect (1–3). Concentration-dependent killing refers to the observation that bacterial killing, both *in vitro* and *in vivo,* is maximal with very high serum peaks. Studies also show that peak concentrations of less than 10 times the MIC are associated with the emergence of resistance (4–6). In addition, the growth of surviving bacteria is suppressed throughout the dosing interval despite levels that fall below the MIC; no benefit is achieved by maintaining levels at or above the MIC during the entire dosing interval. The duration of this postantibiotic effect increases with increasing peak concentration. *In vitro* and *in vivo* animal studies also show that microorganisms temporarily down-regulate aminoglycoside uptake for several hours after exposure. This property is known as microorganism-adaptive resistance.[2] Giving aminoglycosides during this period of adaptive resistance diminishes killing potential. These three principles form the rationale for the extended-interval dosing regimen for aminoglycosides.

Animal and human nephrotoxicity models demonstrate that increased aminoglycoside cortical tissue concentration correlates with nephrotoxicity (3). Extended-interval aminoglycoside dosing results in lower cortical tissue levels than does divided dosing because of the saturable kinetics of aminoglycoside uptake. Lower mean serum drug concentrations per length of dosing interval occur with the extended-interval regimen. Studies of the kinetics of cochlear tissue uptake are incomplete, and their results are conflicting.

Trials

Several trials document that extended-interval dosing of aminoglycosides is as effective as multiple-daily dosing. Some results show either decreased or delayed development of nephrotoxicity (7–9). A recent meta-analysis of 21 randomized trials involving 3091 patients was published (10). This meta-analysis compared outcomes in patients receiving the same total dose of aminoglycosides administered daily and those who received doses several times per day. They concluded that once-daily aminoglycoside dosing is at least as effective as multiple-daily dosing and is associated with less risk of nephrotoxicity (10). The pooled data show a risk ratio of 0.74 for nephrotoxicity for daily dosing of aminoglycosides (10).

There are insufficient data to support the use of the extended-interval dosing regimen for infants and for patients with endocarditis, as well as for those with endstage renal failure who are undergoing dialysis. The data are currently unclear regarding the efficacy of extended-interval aminoglycosides in patients with cystic fibrosis and neutropenia. Aminoglycoside pharmacokinetics may be altered in patients with anasarca, and those with burns over more than 20% of their body surface area. In these situations, serum levels attained by extended-interval dosing are unpredictable. Use of aminoglycoside in pregnancy is complicated by high rates of fetal ototoxicity and is generally contraindicated.

---

[2] Pharmacy newsletter of the Jewish Hospital of St. Louis, MO. Infrequent Dosing Schedule for Aminoglycosides. Medical Therapeutics of the Jewish Hospital of St. Louis, MO 1994; January–February 6(4/5):1–5.

The results in selected human trials are summarized in Table 1. All summarized trials involved adult or elderly immunocompetent individuals who had infections with Gram-positive or Gram-negative microorganisms. The selected data indicate no difference in efficacy between extended-interval and divided dosing with the exceptions of Giamarellou (see reference in Table 1, improved efficacy with once-daily dosing) and Maller et al. (see reference in Table 1, no report of efficacy). Nephrotoxicity in the extended-interval groups was either similar to or less than in the

TABLE 1

Selected Human Trials[a]

Reference	Drug	Other Drugs	Mean Age (range)	Patients (n)	Design[b]	Dosage	Toxicity
Reichley et al. (1995)[c,d,e] (ref. 7)	Gent	Not stated	67	432	O,P	5 mg/kg IV qd, q36h, q48h	5.8% of 346, NT
	Gent		67	485		avg 875 mg IV, divided	14.8% of 398, NT
Reichley et al. (1995)[c] (ref. 8)	Gent	Not stated	55	227	O,P	5 mg/kg IV	13/209, NT
	Gent		53	486		avg 740 mg IV, divided	10/377, NT
Nicolau et al. (1995)[d] (ref. 9)	Gent	Not stated	46 (13–97)	2,184	O,P	7 mg/kg IV, divided	27/2184, NT 3 patients, OT
Maller et al. (1988) (ref. 12)	Amik	β	67	16	R,P	11 mg/kg IV qd	0/16, NT
	Amik		65	14		15 mg/kg IV qd	1/14, NT
	Amik		64	15		7.5 mg/kg IV qd	0/15, NT
Vanhaeverbeek et al. (1993) (ref. 13)	Amik	F, β, Clin	69	19	O,P	5 mg/kg IV qd	0/19, NT
	Amik		63	20		7.5 mg/kg IV qd	1/20, NT
Prins et al. (1993)[e] (ref. 14)	Gent	Am	59 (17–89)	59	R,O,P	4 mg/kg IV qd	2/40, NT; 7/12, OT
	Netil		59 (27–87)	64		1.33 mg/kg IV tid	11/45, NT; 6/11, OT
Prins et al. (1994) (ref. 15)	Gent	Am	N/A	93	R,O	4 mg/kg IV qd	5/72, NT; 8/15, OT
	Netil		N/A	82		5.5 mg/kg IV qd	10/69, NT; 7/15, OT
Ter Braak et al. (1990) (ref. 16)	Netil	Cef	71 (18–92)	69	R,O,P	3.9 mg/kg IV qd	9/61, NT; 2/32, OT
	Netil		70 (17–89)	72		3.8 mg/kg IV, divided	11/66, NT; 1/31, OT
Sturm (1989) (ref. 17)	Netil	None	59 (18–87)	35	R	6 mg/kg IV qd	1 patient (qd group) with NT; no patients with OT
	Netil		64 (23–88)	35		2 mg/kg IV tid	Total of 69 patients followed up for NT; 35 patients followed up for OT
Nordstrom et al. (1990) (ref. 18)	Gent	Not stated	58	14	R,O,P	4.5 mg/kg IV or IM qd	5/14, NT; 1/12, OT
	Gent		60	14		1.5 mg/kg IV or IM tid	5/12, NT; 0/12, OT
	Netil		53	15		4.5 mg/kg IV or IM qd	5/15, NT; 0/8, OT
	Netil		61	13		1.5 mg/kg IV or IM tid	4/13, NT; 0/11, OT
Labovitz et al. (1974) (ref. 19)	Gent	Not stated	53 (22–80)	11	O	160 mg IM qd	6/11, NT
	Gent		40 (20–74)	10		60–180 mg IM tid	2/10, NT
Giamarellou (1991) (ref. 20)	Amik	β	56 (20–76)	30	O,R	15 mg/kg IV qd	Few had NT and/or OT; <5 patients in each group
	Amik		59 (23–81)	30		7.5 mg/kg IV bid	

---

[a] In most studies listed, there was no difference in efficacy. Giamarellou reported better efficacy in the once-daily group. Maller et al. did not report efficacy. Abbreviations used are: Amik, Amikacin; Am, Amoxicillin; β, β-Lactam; Cef, Ceftriaxone; Cli, Clindamycin; F, Flagyl; Gent, Gentamicin; Netil, Netilmicin; NT, nephrotoxicity; OT, ototoxicity. The format was adapted from references 2 and 3 with recent information added.

[b] O, open; P, prospective; R, randomized.

[c] Published as an abstract. In reference 8, the rate of nephrotoxicity apparently is increased in the extended-interval group as compared with the divided-dosing group. The authors explain this finding by noting an increased prevalence of intensive care patients in the extended-interval group. In multivariate analysis, the authors do not find a statistically significant association between the type of dosing interval and nephrotoxicity, but do find a statistically significant association between intensive care and nephrotoxicity ($p = 0.008$).

[d] Data were collected concurrently from groups of patients in all studies except in the studies of Reichley et al. (7) and of Nicolau et al. (9) in the Nicolau study, the hospital historical rate of nephrotoxicity was 3.5%, whereas in the Reichley study, the hospital historical rate of nephrotoxicity was 14.8%.

[e] The statistically significant difference for nephrotoxicity is as follows: Reichley et al. (7), $p < 0.001$; Prins et al. (14), $p = 0.016$.

divided-dosing groups. Two studies (noted below) had statistically significant lower rates of nephrotoxicity in their respective extended-interval groups. Reichley et al. (8) showed increased nephrotoxicity in the extended-interval group of one of their comparisons. This finding was attributed to an increased proportion of intensive care patients in that particular extended-interval group. Ototoxicity was not assessed uniformly.

Dosing Nomogram

Extended-interval aminoglycoside dosing uses a fixed dose given at varied dosing intervals. Dosing is either daily or at longer intervals of 36 or 48 hours. For the first dose, the dosing interval is chosen based on an estimate of the creatinine clearance (C_{Cr}). A nomogram[2] (Fig. 1) is used to adjust the dosing interval. Multiple nomograms exist (9). The steps are:

a. Initially, estimate the creatinine clearance as per Tables 2 and 3, or measure the rate of urinary excretion of creatinine over a 2- to 4-hour interval or from a 24-hour urine collection. In the presence of significant edema, the creatinine clearance should be measured rather than estimated.
b. Based on this initial estimate or measurement of creatinine clearance, an initial dosing interval is chosen (Table 4).
c. The fixed doses are: Gentamicin/Tobramycin/Netilmicin, 5 mg/kg of body weight; Amikacin, 15 mg/kg of body weight.
d. A determination of random serum drug levels is obtained 6 to 14 hours after the first dose.
e. This random level is compared with the nomogram (Fig. 1) to determine the final dosing interval. When serum drug levels exceed the values for a particular dosing interval as shown in the nomogram, the dosing interval must be adjusted. For example, an initial dosing interval of every 24 hours for gentamicin would be changed to a dosing interval of every 36 hours if the first serum drug level at time 10 hours was 5 µg/mL. Thus, the second dose of the drug would be given at time 36 hours, instead of time 24 hours, at the same dose of 5 mg/kg. A repeat serum drug level then would be checked 6 to 14 hours later.
f. Repeat random serum drug levels are obtained one to two times weekly and compared with the nomogram (Fig. 1) once a stable drug level has been achieved.

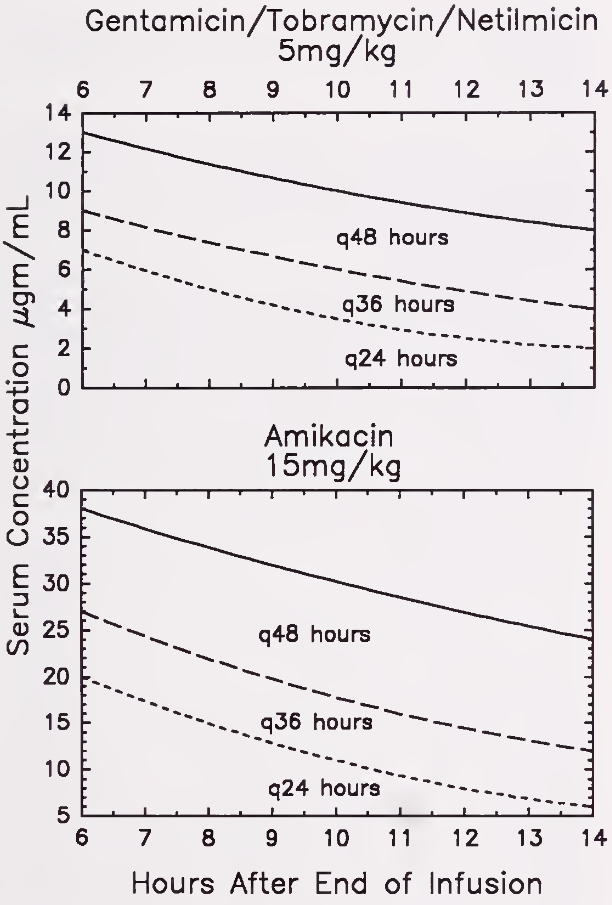


Fig. 1. Extended interval monogram. To determine the dosing interval for the aminoglycosides, a random serum drug level is obtained between 6 and 14 hours after the initial intravenous infusion. The plot indicates whether once daily (24 hours), every 36 hours, or every 48 hours should be the dosing interval. When serum drug concentrations exceed the values depicted for the upper curves in each graph, the drug should be administered every 8 hours according to conventional methods with more frequent drug level monitoring. Otherwise, repeat random serum drug levels are obtained once or twice weekly to ensure appropriate interval dosing.

Cost Considerations

Aminoglycosides are not costly. Their use in conjunction with other agents adds marginally to the total cost of antibiotic therapy. In addition, extended-interval dosing is more cost effective than multiple-daily dosing. The factors that account for this cost efficiency include: (i) decreased

TABLE 2
Creatinine Clearance Calculation (11)[a]

C_{Cr} (male) =	$\dfrac{(140 - \text{age})(\text{Wt})}{S_{Cr}\ (\text{mg/dL}) \times 72}$
C_{Cr} (female) =	C_{Cr} (male) × 0.85

[a] C_{Cr}, creatinine clearance; S_{Cr}, serum creatinine; Wt, actual body weight or estimated dry weight (kg) if patient is edematous. Use the obese dosing weight (ODW = Wt − 0.6 [Wt − bw]) when the patient is judged to be obese. bw = "acceptable" weight. (See Table 3.)

TABLE 3

Relationship of Life Insurance Weight and "Acceptable Range," "Overweight," and "Obese" for Men and Women and Quetelet's Index (QI) (kg/m^2)

	Acceptable Range		Overweight		Obese	
Height (m)	Wt (kg)	QI	Wt (kg)	QI	Wt (kg)	QI
Men						
1.6	44–65	17–25	72	28	78	30
1.7	51–73	18–25	80	28	88	30
1.8	58–80	18–25	88	27	96	30
1.9	66–90	18–25	99	27	108	30
Women						
1.5	38–55	17–24	61	27	66	29
1.6	41–59	16–23	65	25	71	28
1.7	45–66	16–23	73	25	79	27
1.8	52–74	16–23	81	25	89	27

Reproduced from J. S. Garrow In: D. J. Weatherall, J. G. G. Ledingham, and D. A. Warrell, editors. Oxford Textbook of Medicine. 3rd ed. Oxford, New York, Tokyo: Oxford University Press; 1996. p. 1302, with permission.

TABLE 4

Initial Dosing Interval

Creatinine Clearance (mL/min)	Dosing Interval (hr)
>60	24
40–59	36
20–39	48
<20	Do not use nomogram. Doses should be reduced.

laboratory measurement costs, (ii) decreased nursing time, and (iii) decreased use of intravenous bags and tubing. Estimates of the drug cost for 10 days of intravenous therapy are as shown in Table 5.

Another consideration is the potential savings made possible by replacing monotherapy with combination therapy that includes aminoglycosides. For example, consider the drug costs of two different empiric regimens of intravenous therapy for pyelonephritis. The cost of using Ampicillin, 2 g every 6 hours, and Gentamicin, 350 mg daily, is $70 whereas that of Ampicillin/Sulbactam, 1.5 g every 6 hours, is $234.

TABLE 5

Drug Costs

Gentamicin, 350 mg IV qd	18
Gentamicin, 80 mg IV q8h	44
Tobramycin, 350 mg IV qd	140
Tobramycin, 80 mg IV q8h	109
Amikacin, 1050 mg IV qd	257
Amikacin, 350 mg IV q8h	407
Ampicillin, 2 g IV q6h	51
Cefazolin, 1 g IV q8h	112
Ampicillin/Sulbactam, 1.5–3 g IV q6h	234–415
Cefuroxime, 750 mg–1.5 g IV q8h	182–346
Cefoperazone 2 g IV q12h	518
Cefotetan, 1–2 g IV q12h	202–378
Ceftriaxone, 1–2 g IV q24h	252–486
Ceftazidime, 1–2 g IV q8h	339–644
Ciprofloxacin, 400 mg IV q12h	439

Based on estimates, assuming a body weight of 70 kg, from the Mount Sinai Master Listing, 12/30/95. These figures reflect drug costs in dollars and do not include estimates of nursing and administrative costs.

Summary

Aminoglycosides are efficacious additives in the therapy of aerobic Gram-negative bacterial infections. Synergy with cell-wall active agents against Gram-positive bacteria is a well-described benefit. Aminoglycosides can be used in combination with other agents against *Pseudomonas, Klebsiella, Enterobacter, Serratia,* viridans streptococci, enterococci, and some staphylococcal species.

The benefits of using aminoglycosides include: (i) low rates of resistance and resistance-emergence, (ii) potential for decreasing β-lactam resistance, (iii) rare allergenicity, and (iv) relatively low cost.

Extended-interval dosing of aminoglycosides does not sacrifice efficacy and is not associated with higher rates of toxicity. Extended-interval dosing may be associated with decreased toxicity. Extended-interval aminoglycosides dosing is not well supported for use in endocarditis, hemodialysis, infancy, and patients with anasarca or burns over more than 20% of the body surface area. Its use in patients with cystic fibrosis and neutropenia deserves further study. The use of extended-interval aminoglycosides in pregnancy is associated with high risks of ototoxicity to the fetus.

Extended-interval dosing is based on pharmacodynamic principles of concentration-dependent killing, postantibiotic effect, and adaptive resistance. Extended-interval dosing uses fixed doses of 5 mg/kg of gentamicin/tobramycin/netilmicin and 15 mg/kg amikacin. Initial dosing interval for the aminoglycosides should be based on estimates and/or measurements of creatinine clearance. Subsequent dosing intervals can be guided by the above nomogram.

Aminoglycosides may see increasing future usage as bacterial resistance to other agents continues to increase.

References

1. Mandell G, Bennett J, Raphael D. Aminoglycosides. In: Mandell G, Douglas T, and Bennett J, editors. Prin-

ciples and practice of infectious diseases. 4th ed. New York: Churchill Livingstone; 1995. p. 279–306.

2. Preston S, Briceland L. Single daily dosing of aminoglycosides. Pharmacotherapy 1995; 15:297–316.
3. Bates R, Nahata M. Once-daily administration of aminoglycosides. Ann Pharmacother 1994; 28:757–766.
4. Blaser J, Stone B, Groner M, Zinner S. Comparative study with enoxacin and netilmicin in a pharmacokinetic model to determine the importance of ratio of antibiotic peak concentration to mic for bactericidal activity and emergence of resistance. Antimicrob Agents Chemother 1987; 31:1054–1060.
5. Gelber A, Vastola A, Brandel J, Craig W. Selection of aminoglycoside resistant variants of *Pseudomonas aeuroginosa* in an *in vitro* model. J Infect Dis 1982; 146:691–697.
6. Pechere J, Marchou B, Michea-Hamaphour M, Auckenthal R. Emergence of resistance after therapy with antibiotics used alone or combined in a murine model. J Antimicrob Chemother 1986; 17 (Suppl A):11–18.
7. Reichley R, Little J, Bailey T. Advantages of extended interval aminoglycoside dosing in a predominantly elderly population. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, Sep 1995, Abstract A118.
8. Reichley R, Abraham M, Little J, Bailey T. Prospective evaluation of extended-interval aminoglycoside dosing at a 1200-bed institution. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, Sep 1995, Abstract A117.
9. Nicolau D, Freeman C, Belliveau P, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 1995; 39:650–655.
10. Barza M. Single or multiple daily doses of aminoglycosides: a meta-analysis. BMJ 1996; 312:338–345.
11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41.
12. Maller R, Isaksson B, Nilsson L, Soren L. A study of amikacin given once versus twice daily in serious infections. J Antimicrob Chemother 1988; 22:75–79.
13. Vanhaeverbeek M, Siska G, Douchamps J, Herchuelz A. Comparison of the efficacy and safety of amikacin once or twice-a-day in the treatment of severe gram-negative infections in the elderly. Int J Clin Pharmacol Ther Toxicol 1993; 31:153–156.
14. Prins JM, Buller HR, Kuijper EJ, et al. Once versus thrice daily gentamicin in patients with serious infections. Lancet 1993; 341:335–339.
15. Prins JM, Buller HR, Kuijper EJ, et al. Once-daily gentamicin versus once-daily netilmicin in patients with serious infections: a randomized clinical trial. J Antimicrob Chemother 1994; 33:823–835.
16. Ter Braak EW, de Vries PJ, Bouter KP, et al. Once-daily dosing regimen for aminoglycoside plus β-lactam combination therapy of serious bacterial infections: comparative trial with netilmicin plus ceftriaxone. Am J Med 1990; 89:58–66.
17. Sturm AW. Netilmicin in the treatment of gram-negative bacteremia: single daily versus multiple daily dosage. J Infect Dis 1989; 159:931–937.
18. Nordstrom L, Ringberg H, Cronberg S, et al. Does administration of an aminoglycoside in a single daily dose affect its efficacy and toxicity? J Antimicrob Chemother 1990; 25:159–173.
19. Labovitz E, Levinson ME, Kaye D. Single-dose daily gentamicin therapy in urinary tract infection. Antimicrob Agents Chemother 1974; 6:465–470.
20. Giamarellou H, Yiallouros K, Petrikkos G, et al. Comparative kinetics and efficacy of amikacin administered once or twice daily in the treatment of systemic gram-negative infections. J Antimicrob Chemother 1991; 27(Suppl C):73–79.

Pediatrics at Mount Sinai

Donald Gribetz, M.D.

Abstract

The Department of Pediatrics at The Mount Sinai Hospital was founded more than 120 years ago. During the ensuing years it had five outstanding leaders, Drs. Abraham Jacobi, Henry Koplik, Bela Schick, Horace Hodes, and Kurt Hirschhorn. The evolution of its beginning as a "small" clinic to its present position as one of the outstanding pediatric centers in this country reflects its interest in and devotion to the care of children. **Key Words:** pediatrics, Mount Sinai

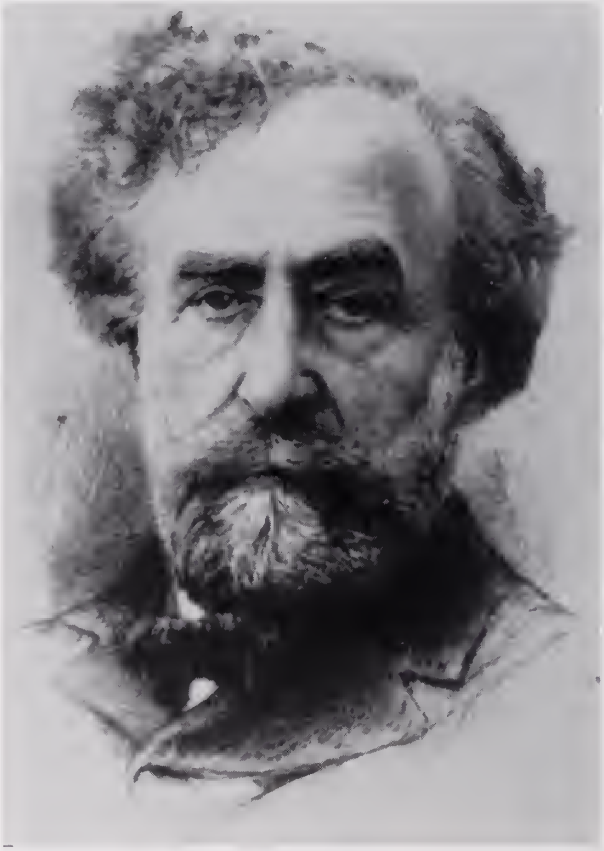


Fig. 1. Abraham Jacobi

The Mount Sinai Hospital, known originally as Jews Hospital, was established in New York City in 1852 (1). There were no separate pediatric activities until 1860. Abraham Jacobi (Fig. 1), born in Germany in 1830, escaped from the Prussians during the Revolution of 1848 and came to the United States in 1853. He had finished his medical studies at several medical schools, as was customary at that time in Europe. He had already written, together with obstetrician Emil Noeggerath, a text, "Contributions to Midwifery and Diseases of Women and Children." After practicing privately in New York City for 7 years, he was appointed Attending Physician at Jews Hospital in 1860. In that same year he was appointed to the Special Chair of Diseases of Children at the New York Medical College (not related to the current institution with the same name). This was the first pediatric clinic in the United States. He suggested pediatrics as a scientific as well as a clinical speciality (2). In the ensuing years he accepted two other appointments, one at the University of New York in 1865 as clinical chair and Professor of Pediatrics, and the other at the College of Physicians and Surgeons in 1870, first as Clinical Professor of Pediatrics and later as Professor and Chair (3). He served in these various capacities at that institution for 29 years. All of his activity was concurrent with his service at Jews Hospital, later to be known as The Mount Sinai Hospital.

In 1866, the name Jews Hospital was formally changed to The Mount Sinai Hospital. In 1872, the hospital moved from its first site on

---

Address correspondence to Dr. Donald Gribetz, Professor of Pediatrics, Department of Pediatrics, The Mount Sinai School of Medicine, One East 100th Street, Box 1205, New York, NY 10029.

28th Street and 8th Avenue to a much larger building on 66th Street and Second Avenue. In 1875, the Children's Department in the Dispensary at Mount Sinai was organized similarly to the one at New York Medical College (1), and was placed under the leadership of Dr. Mary Putnam (Fig. 2). She had earlier gone to the Female Medical College in Pennsylvania and became the sixth woman to graduate from any medical school in the United States. She sought additional training at and was the first woman graduate of l'École de Médecine in Paris. She returned to the United States in 1871. She and Dr. Jacobi married in 1875 and together they wrote a book "Infant Diet," which became the "Spock" of those days (2). In 1878, because of the inadequacy of the Children's Department facilities in the Dispensary to care for the great numbers of children referred to the hospital, a formal pediatric service was established within The Mount Sinai Hospital. This pediatric service was the first in New York and one of the first in the United States. Its creation and maintenance was made possible by a legacy left to the hospital by Michael Reese of California. Jacobi was appointed Hospital Pediatrician in 1879 and served as Director until 1893. In addition to his busy clinical and teaching activities, he was very active in "organized medicine." He was president of the New York Medical Society, the New York Academy of Medicine, and the American Medical Association. He was always a prime sponsor of children's rights and promoted their health care. He remained as Consulting Pediatrician until his death in 1919. He is recognized to this day as the father of pediatrics in the United States. To further honor his name in 1952, at the one hundredth anniversary of the founding of The Mount Sinai Hospital, the Jacobi Medallion was established to honor those Mount Sinai physicians and lay persons who had achieved distinction in medicine and/or provided exceptional service to the Alumni and The Hospital.

Dr. Barnim Scharlau was appointed to succeed Dr. Jacobi as chief of the service in 1893. He served with exemplary diligence until 1900 (4) at which time Dr. Henry Koplik (Fig. 3), who had been Adjunct Visiting Physician to the Children's Service since 1891, was appointed Attending Pediatrician to the Children's Service (5, 6). In 1887, Dr. Koplik had been appointed Attending Physician to the Good Samaritan Dispensary which was located in lower Manhattan. This clinic served as a model for the care of a very large population of infants and children. In 1889, Dr. Koplik founded the first station for the distribution of sterilized milk in the United States (7) at The Good Samaritan Dispensary where, by then, he served as director. In 1898, Dr. Koplik described the diagnostic spots of measles in the buc-

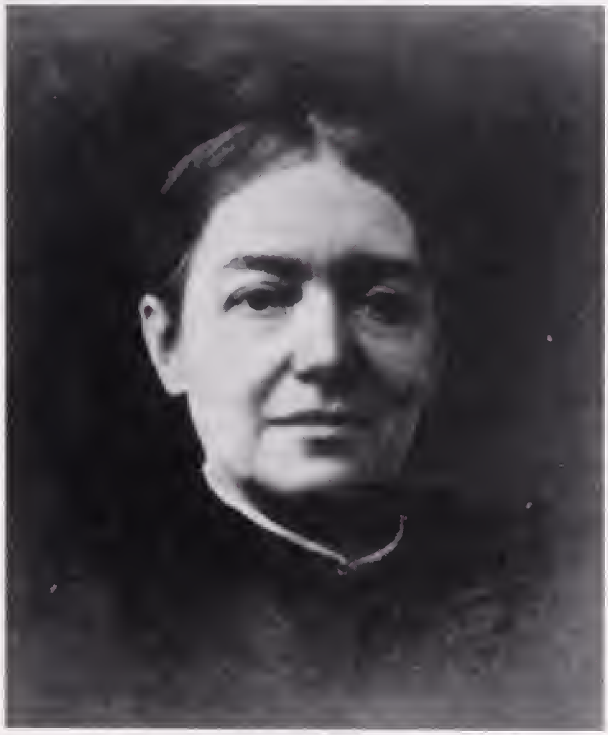


Fig. 2. Mary Putnam

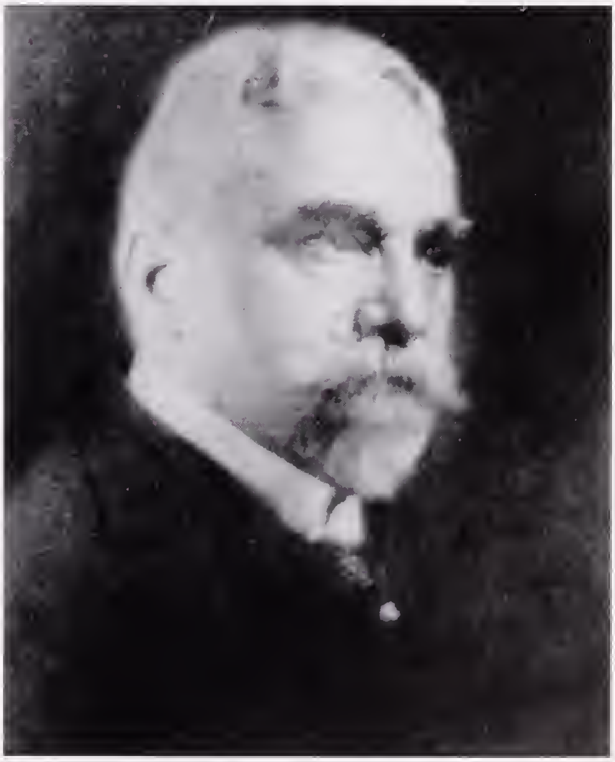


Fig. 3. Henry Koplik

Fig. 4. Bela Schick

cal mucous membranes which, to this day, bear his name (8). He was one of the first pediatricians to interest himself in bacteriology, and he conducted fundamental studies on diphtheria and pertussis organisms. He was an outstanding clinician, and was strict and demanding of his trainees. He was one of the founders of the American Pediatric Society and served as its president. He retired from The Mount Sinai Hospital in 1925 after having given 34 years of distinguished service. He died in 1927.

When The Mount Sinai Hospital moved to its third home on Fifth Avenue between 100th and 101st Streets in 1904, a Children's Pavilion, funded by Henry Einstein in memory of his son Lewis, was built. Innovations included cheerful wards, play spaces, a solarium on the roof, and a view of Central Park.

Two children's diseases were described at The Mount Sinai Hospital during this period. Although neither discoverer was a pediatrician, these conditions led to much research. The first was a degenerative disease of infants described by Dr. Warren Tay, a British ophthalmologist (9). Almost simultaneously, Dr. Bernard Sachs, the first Attending Neurologist at The Mount Sinai Hospital, also described the disease (10). To this day the disease is known as Tay-Sachs Disease. The second disease was nephrosis, described by Dr. Albert Epstein of the newly organized Pathology Department. This kidney disease also bears the name of its describer (11).

Another "first" emanating from The Mount Sinai Hospital's Department of Pediatrics was created by Dr. Ira Wile who joined the staff in 1904. He became interested in child psychiatry and thus developed extensive activities in behavior, social problems, and children's education. In 1919, he opened the first child guidance clinic in the United States. It was called the Children's Health Class, and it became the first channel through which preventive medicine was integrated on an equal footing with the rest of the pediatric work of the hospital. Dr. Wile stated that the "Class is founded on the positive idea of health rather than the negative idea of disease." He further stated prophetically that "the attention of the clinic is directed chiefly to the periodic examination of children between infancy and school age. This is a period during which the health of poorer children is commonly neglected and when physical and psychological mismanagement may readily implant the seeds of disease against which the Department of Health and other agencies subsequently struggle in vain." These seminal ideas were further publicized in subsequent papers and meetings (12).

In 1923, the Hospital invited Dr. Bela Schick (Fig. 4), a pediatrician of renown in Europe, to come to this country and serve as Pediatrician to the Hospital. He had already done his groundbreaking work with Von Pirquet on antigen/antibody reactions which laid the foundation for immunity and hypersensitivity (13). In fact, they coined the term allergy. Dr. Schick also had done his seminal work on diphtheria, developing a skin test with toxin from diphtheria organisms (14). This procedure was the first of many skin tests used to determine whether a child was immune or susceptible. These contributions rank as great achievements in medicine and have provided an understanding of immunity to infection. In the book *Bela Schick: The World of Children,* Renée Dubois is quoted: "to hundreds of millions of men over the whole planet, the name Schick calls to mind not a person but merely a scratch on the arm to test susceptibility to diphtheria. Bela Schick must resign himself to reduce or magnify his name to a common household word, one of almost universal usage." (15).

Dr. Schick remained Chief of Pediatrics at

Fig. 5. Murray Bass

The Mount Sinai Hospital until 1942. His rounds were characterized by continuous stimulation of his younger colleagues, his searching approach to problems at the bedside, and his exemplary behavior to the infants and their parents. He received the John Howland Award, the highest award in pediatrics, the Gold Medal of the New York Academy of Medicine, and the Jacobi Medallion.

Another pediatrician, Dr. Jean Pakter, was the first woman to complete a medical/surgical internship at The Mount Sinai Hospital in 1934–1935. Her 35 years of professional life were devoted to the care and study of newborns, especially those who were premature. With her colleagues she published many papers directed toward reducing mortality of these babies. She developed the reputation of actually nurturing her small charges, and her ideas were taken up by future neonatologists (16, 17).

Of great importance during this period was a bequest of $950,000 made to the hospital by Dr. Sarah Welt, a pediatrician closely affiliated with the Pediatric Department. She set up the Sarah Welt Fellowship in Research Medicine and a loan fund for young physicians who needed financial help. She also contributed to the Baby Clinic. In fact, I received a Sarah Welt Fellowship for several years when I was appointed in 1953.

Between Dr. Schick's retirement in 1942 and the appointment of Dr. Horace Hodes as the first full-time Chief of Pediatrics in 1948, Dr. Murray Bass (Fig. 5), a superb and highly respected clinician, served as acting chief. Dr. Bass was a pediatrician beloved by his patients and their families. At ward rounds he was stimulating, inspiring, and instructive. His bibliography was characterized by concern for urgent practical problems in children. He published articles on lead poisoning from neonatal nipple shields, vitamin A deficiency in infants, and periorbital edema in infectious mononucleosis (19, 20). When he retired as director of the service in 1948, he remained in private practice until 1960. He, too, was awarded the Jacobi Medallion. The "Friends of Murray Bass" raised funds for the Murray Bass Attending Pediatrician for Research.

Another clinician and teacher during these interim years was Dr. Samuel Karelitz (Fig. 6). Drs. Karelitz and Schick were the first to suggest that fluids be administered intravenously to in-

Fig. 6. Samuel Karelitz

Fig. 7. Horace Hodes

fants who were dehydrated (21). Dr. Karelitz was a Lieutenant Colonel in the Army and was the commander of Mount Sinai's Army Unit in World War II. In addition to their active pediatric practices, Drs. Bass and Karelitz developed a cadre of clinicians including Drs. Jerome Kohn, Alfred Fischer, George Ginandes, Samuel Delange, Sidney Blumenthal, and Ralph Moloshok among others. These experienced pediatricians and the younger colleagues whom they nurtured made the Pediatric Department an outstanding clinical group and a haven for consultation referrals from the entire city and the surrounding suburbs. Dr. Karelitz, in addition, was very active in the American Academy of Pediatrics, a national society, serving on committees. He stimulated the development of standards to guide pediatricians and prospective adoptive parents and was awarded the Clifford Grulee Award, the highest award of the Academy, and the Jacobi Medallion.

By 1948 The Mount Sinai Hospital decided to commit more of its resources to its development as an academic health center. With the arrival of Dr. Hodes (Fig. 7) as the first full-time Chief of Pediatrics, the department flourished in many ways. He had served as the physician in charge of the Sydenham Hospital for Infectious Diseases in Baltimore. While there, he reported his work on the virus of diarrhea, the first such agent to be identified as a cause of diarrhea in humans (22). For this seminal work, he received the prestigious Mead Johnson Award for Research in Pediatrics in 1946. I had the good fortune of spending three months with him in Baltimore before his arrival at Mount Sinai. Going on rounds each morning and hearing him describe measles, meningitis, and scarlet fever was an unforgettable experience. To watch him perform a tracheostomy on a patient with polio in an iron lung was an eye-opener.

At The Mount Sinai Hospital, shortly after his arrival, he opened a respirator center for patients with polio. Ten to fifteen iron lungs were always filled with paralyzed patients, who were seen by him almost daily. He quickly became involved in the organization and preparation for a medical school, the Mount Sinai School of Medicine which was chartered in 1966. His continuing research at Mount Sinai involved further identification of the polio virus, the nature of polio virus in breast milk, and the characteristics of endotoxin. In addition to his laboratory work, he was an outstanding teacher and a superb clinician. When I called him and said "I had a child with an unusual rash," his answer was "I'll be in your office in 5 minutes." I considered myself fortunate indeed to have my office in the hospital. He was a pediatrician, who combined excellence in research, teaching, and clinical skills. To this day, I do not know which he enjoyed most. He stimulated studies on the administration of penicillin to all newborns in the delivery room to prevent Group B streptococcus infection, which the newborns could contract from infected mothers. When this was shown to be effective by his colleague, Dr. Alex Steigman (23), many newborn services in the United States adopted the procedure. He invited Dr. Richard Day, who was retiring from the Columbia College of Physicians and Surgeons, to join our service and set up a modern newborn nursery. He urged Dr. Ralph Moloshok to continue his studies on a newly discovered disease, familial dysautonomia (also known as Riley-Day syndrome). Both Drs. Hodes and Day served as President of the Society of Pediatric Research and the American Pediatric Society. Both received the John Howland Award from the American Pediatric Society. Dr. Hodes and Dr. Moloshok each received the Jacobi Medallion and both have their names assigned to classrooms and libraries in our department.

When Dr. Hodes retired in 1977, he was suc-

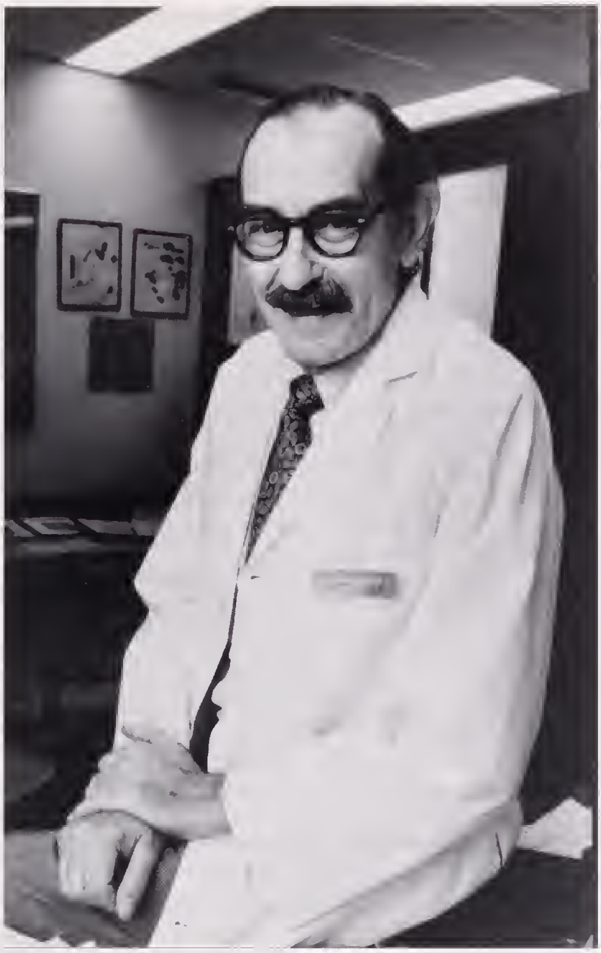


Fig. 8. Kurt Hirschhorn

ceeded by Dr. Kurt Hirschhorn (Fig. 8), who moved from his position as Professor and Chief of the Division of Genetics. Dr. Hirschhorn is a recognized authority on biochemical and molecular genetics. He has also made fundamental discoveries in lymphocyte reactions in the field of immunology and has described several clinical and metabolic inborn errors. His name has been attached to the Hirschorn-Wolf syndrome which he was instrumental in describing (24, 25). He served as President of the American Society of Genetics and was an active member of the Hastings Center for Biomedical Ethics. He, too, received the Jacobi Medallion. Dr. Hirschhorn continued his predecessor's role of teaching, research, and clinical activities. He enlarged the department by adding new clinical and research divisions. He retired in 1995.

Dr. Frederick J. Suchy (Fig. 9), most recently from Yale University School of Medicine, has now assumed the leadership of the department. He is an internationally recognized pediatric gastroenterologist. He has edited the definitive text on liver diseases in children (26). His several prestigious research awards include the American Liver Foundation Pediatric Research Prize and the Excellence in Research Award from the American Academy of Pediatrics. He has already indicated that he plans to carry on in the tradition of Drs. Hodes and Hirschhorn in the primary care of children and in research in pediatrics.

To summarize, in 1996, 144 years after the founding of The Mount Sinai Hospital, the Pediatric Service consists of 72 ward beds, 55 healthy newborn bassinets, 8 intensive care beds, and 35 intensive care newborn beds. The department has 17 subspeciality divisions with 71 full-time faculty and an additional voluntary cadre of 40 practicing pediatricians. This combined faculty teaches 50 pediatric house officers and 25 fellows. In addition, 30 years after starting a new medical school, there are 500 candidates studying for the M.D. degree and 175 candidates studying for the Ph.D. degree, many of whom are based in the Department of Pediatrics. This is quite a change from the very small beginning in pediatrics 120 years ago. The effort of all these people at Mount Sinai attests to the priority assigned to the continuing care, health, and development of children.

Fig. 9. Frederick Suchy

References

1. Hirsch J, Doherty B. The Mount Sinai Hospital of New York, 1852–1952. New York: Random House; 1952.
2. Pelner L. Abraham Jacobi, M.D. 1830–1919. NY State J Med 1970; 70(17):2237–2241.
3. Jacobi A. History of pediatrics in New York. Arch Pediatr 1917; 34:1–11.
4. Gerster A. Recollections of a New York surgeon. New York: Paul B. Hoeber; 1917.
5. Libman E. Obituary: Dr. Henry Koplik. Bull N Y Acad Med 1927; 3:667–671.
6. Bass MH. Henry Koplik (1858–1927). J Pediatr 1955; 46: 119–125.
7. Koplik H. The sterilization of milk at low temperatures and the equipment of milk laboratories for infant feeding. NY Med J 1891; 55:121–125.
8. Koplik H. The diagnosis of the invasion of measles from a study of the exanthem as it appears on the buccal mucous membranes. Arch Pediatr 1896; 13:918–922.
9. Tay W. Symmetrical changes in the region of the yellow spot in each eye of an infant. Trans Ophthalmol Soc UK 1881; 1:55–57.
10. Sachs B. On arrested cerebral development with special reference to its cortical pathology. J Nerv Ment Dis 1887; 14:551–553.
11. Epstein AA. Concerning the causation of edema in chronic parenchymatous nephritis and method for its relief. Med Rec NY 1917; 91:128.
12. Wile IS. Physical problems of abnormal behavior. Read before NY Physicians Association section of the Academy of Medicine. October 20, 1927.
13. Von Pirquet C, Schick B. Die Serumkrankheit. Vienna, Leipzig: Deuticke; 1905.
14. Schick B. Die Diphtherietoxin-Hautreaktion des Menschen als Vorprobe der prophylaktischen Diphtherieheilserum injektion. München med Wchnschr 1913; 60: 2608–2610.
15. Goronowicz A. Bela Schick and the world of children. New York: Abelard and Schuman; 1954.
16. Pakter J, Jacobziner H. A five year review of the premature infant program. NY City Department of Health. NY State J Med 1954; 54:3207–3214.
17. Pakter J, Nelson F. Factors in the unprecedented decline in infant mortality in New York City. Bull NY Acad Med 1974; 50:839–868.
18. Bass MH, Blumenthal S. Fatal lead poisoning in nursing infant due to prolonged use of lead nipple shields. J Pediatr 1939; 15:724–732.
19. Bass MH. Periorbital edema as initial sign of infectious mononucleosis. J Pediatr 1954; 45:204–205.
20. Bass MH, Fisch GR. Increased intracranial pressure with bulging fontanelle: A symptom of vitamin A deficiency in infants. Neurology 1961; 2:1091–1094.
21. Karelitz S, Schick B. Treatment of toxicosis with aid of continuous intravenous drip of dextrose solution. Am J Dis Child 1931; 42:781–802.
22. Light JS, Hodes HL. Studies on epidemic diarrhea of the newborn; isolation of filtrable agent causing diarrhea in calves. Am J Public Health 1943; 33:1451–1454.
23. Steigman AJ, Bottone EJ, Hanna BA. Intramuscular penicillin administration at birth: Prevention of early onset group B streptococcal disease. Pediatrics 1978; 62:842–844.
24. Hirschhorn K, Cooper HL, Firschein IL. Detection of short arms of chromosome 4 and 5 in a child with defects of midline fusion. Humangenetik 1965; 1:479–482.
25. Wolf V, Reinwein H, Porsch R. et al. Defizienz an den kurzen Armen eines chromosoms Nr. 4. Humangenetik 1965; 1:397–413.
26. Suchy FJ ed. Liver disease in children. St. Louis: Mosby; 1994.

Current Trends in Onychomycosis Therapy:

A Literature Review

David Hecker, M.D.

Abstract

Problems with the use of griseofulvin and ketoconazole in the treatment of onychomycosis have led to studies of three new oral antifungal drugs to treat this disease: fluconazole, itraconazole, and terbinafine. These drugs have been superior in relation to a high rate of cure, shorter duration of treatment, minimal adverse effects, and prolonged duration of remission. Although both fluconazole and itraconazole are structurally related to ketoconazole, their triazole ring is more site-specific than the imidazole ring of ketoconazole, which makes these newer drugs less likely to cause liver toxicity. Terbinafine belongs to a new class of compounds called the allylamines, which are fungicidal rather than fungistatic. Terbinafine has become the first line of therapy in Europe and Canada for onychomycosis, and it has recently been approved in the United States in oral form. Itraconazole and fluconazole are available in the United States, but fluconazole is not yet approved for treatment of onychomycosis. **Key Words:** onychomycosis therapy, griseofulvin, ketoconazole, fluconazole, itraconazole, terbinafine

Difficulty in safely and effectively treating onychomycosis, particularly of the toenails, using the traditional oral medications griseofulvin and ketoconazole has led researchers to turn to the use of three new oral antifungal drugs for this problem: terbinafine, itraconazole, and fluconazole. The main goals in therapy already have been met in several studies using these drugs, namely, a high rate of cure with shorter duration of treatment and minimal adverse effects. High relapse rates have also plagued those treated with griseofulvin and ketoconazole, and at least short-term follow-up suggests that the duration of remission may be prolonged in a higher proportion of patients with the newer, more effective medications.

It is important to analyze certain nuances in studies on onychomycosis treatment to sufficiently judge the accuracy of these study results. Cure may be defined as a nail clinically cleared of disease, a negative potassium hydroxide (KOH) preparation, a culture negative for fungus, or a combination of these. The time it takes for a dystrophic nail to grow out during treatment is often much longer than the time in which a fungal culture or KOH preparation becomes negative. In fingernails, full growth averages around 6 months, but in toenails it takes 12 to 18 months to replace an entire nail plate (1). Many of the published studies on the treatment of onychomycosis do not follow up patients for 18 months, so that a clinical evaluation of nails may be flawed. Moreover, because fungal cultures may yield false-negative results, it is difficult to distinguish a second new infection from one in which a partially treated infection recurs. It is essential to document whether or not cured patients remain cured long after a study drug is stopped, as well as to indicate if cure lags at all behind the course of treatment used.

From the Department of Dermatology, The Mount Sinai School of Medicine, New York, New York.

Address correspondence to David Hecker, M.D., The Mount Sinai School of Medicine, Box 1048, One East 100th Street, New York, NY 10029-6574.

Griseofulvin

For many years, the gold standard treatment for onychomycosis, griseofulvin, has been disappointing because its cure and relapse rates are not satisfactory. The drug's fungistatic mechanism of action involves a disruption of the formation of microtubules needed in fungal cell mitosis (2). Most studies of griseofulvin, however, have several shortcomings. Total numbers of patients treated are often small, and long-term follow-up usually is not performed. Thus, studies which report high initial cure rates after griseofulvin and provide no recurrent rate are not helpful.

An early study by Kaden (3) in 1964 dealt with these issues. He examined 160 and 200 patients with fingernail and toenail onychomycosis, respectively. Up to 1-g daily of oral griseofulvin resulted in clinical cures of 62% of patients with infected fingernails and 11% of patients with infected toenails. When surgical avulsion of the nails was added as an adjunct to oral therapy, these cure rates improved to 80% and 55%, respectively (n = 46 and 58). After an 18- to 36-month follow-up period, however, recurrence rates were 15% for fingernails and 60% for toenails.

Another study by Davies et al. (4) found a clinical cure in only 12 (40%) of 30 patients treated for 23 months with 1-g daily of oral griseofulvin for fingernail onychomycosis. Mycologic cure (negative KOH preparation and culture), however, occurred in 24 (80%) of the same 30 patients. In patients with infected toenails, only 1 (3%) of 33 were clinically cured and 9 (29%) of 31 were mycologically cured. These findings represent the generally poor efficacy of griseofulvin in onychomycosis, which at the time of the studies above, was the only oral agent available for this problem. In most cases, griseofulvin requires up to 18 months of treatment and high doses for cure. Recurrence rates are high. Dose-dependent adverse effects such as nausea, diarrhea, and headache have also consistently been a compliance problem for this drug, and up to 60% of patients may have such complaints (5).

Ketoconazole

Ketoconazole, an imidazole derivative, has been used as a second line of therapy for onychomycosis. The drug actually has a higher clinical cure rate for toenail fungus than griseofulvin, from 25% reported by Robertson et al. (6), to 72% documented by Galimberti et al. (7). However, reports of hepatotoxicity with this drug have severely limited its use. The possibility that this association is not dose-dependent raises concern about using any dose of ketoconazole (8). Thus, an incidence of hepatotoxicity as high as 1 in 2,000 patients treated with ketoconazole with seven related deaths is mentioned in the literature without definitive proof of a direct drug effect in patients taking multiple medications (9). Nevertheless, ketoconazole has generally been replaced by other oral antifungals.

Fluconazole and itraconazole work in the same way as ketoconazole by inhibiting the demethylation of lanosterol in the synthesis of ergosterol, a vital component of the fungal cell membrane (10). What makes these two new drugs safer, however, is their constituent triazole ring. Unlike ketoconazole's imidazole ring, the triazole ring is very specific for fungal cytochrome P450 activity, but has little effect on human cytochrome P450 (11). This avoids the potential interference with human enzymatic processes and subsequent cell damage which is believed to occur with ketoconazole. Thus the risk of hepatotoxicity is reduced.

Fluconazole

Fluconazole has been widely used as an effective treatment for systemic fungal infections, such as candidiasis, without major side effects. The drug's use strictly for onychomycosis presently is largely anecdotal in the literature, but formal studies on the treatment of this condition are in progress. Such case reports, however, have described a 100% clinical and mycologic cure after 4 to 8 months of therapy, without relapse up to 4 months after treatment (Table 1). One study by Kuokkanen and Alava (12) did investigate the use of 150 mg weekly of fluconazole for up to 12 months, along with topical treatment using 40% urea ointment for nail avulsion. This combination produced a 100% and 92% mycologic cure of fingernail and toenail onychomycosis, respectively, with 100% and 83% cure seen after a 6-month follow-up. Use of 100 mg daily of fluconazole for 6 months with 4 months follow-up in 16 patients was reported to produce clinical cure in 13% and significant improvement in 44% of affected toenails studied (13).

Adverse effects with fluconazole have been reported in as high as 16% of patients studied, mainly limited to gastrointestinal complaints (11.5%), headache (2%), and rash (2%) (14). However, at least one abnormal liver function test was found among 5% of these patients, although

TABLE 1
Treatment Results

Study	Course (months)	Clinical Cure	Mycologic Cure	Clinical Cure	Mycologic Cure
Coldiron (1992), ref. 11				4 mo	
Fluconazole, 100 mg qod Toenails	4–8	2/2	1/1	2/2	
Nahass and Sisto (1993) ref. 37				2 mo	
Fluconazole, 150 mg qwk Fingernails	6	1/1	1/1	1/1	
Hay et al. (1988), ref. 38				6 mo	6 mo
Itraconazole, 100 mg qd	3–8	6/6	6/6	5/6	5/6
Itrazonazole, 100–200 qd Fingernails	3–7	29/45	29/45	29/45	24/45
Itraconazole, 100–200 qd Toenails	5–12	58/80	58/80	49/80	49/80
Arenas et al. (1991), ref. 18					
Itraconazole, 100 mg qd	6	11/12			
Griseofulvin, 500 mg qd Toenails	6	5/15			
Korting et al. (1993), ref. 5				6–12 mo	6–12 mo
Griseofulvin, 660 mg qd	18	2/36	2/36	1/2	1/2
Griseofulvin, 990 mg qd	18	5/36	2/36	2/3	2/3
Itraconazole, 100 mg qd Toenails	18	7/36	3/36	3/3	3/3
Willemsen et al. (1992), ref. 19				6 mo	6 mo
Itraconazole, 100 mg qd	3	3/3	3/3	3/3	3/3
Itraconazole, 200 mg qd Fingernails	3	1/1	1/1	1/1	1/1
Itraconazole, 100 mg qd	3		2/15	9/19	5/19
Itraconazole, 200 mg qd Toenails	3		3/16	11/19	15/19
Goodfield et al. (1992), ref. 22				9 mo	9 mo
Terbinafine, 250 mg qd Fingernails	3	5/7	5/7	5/7	5/7
Terbinafine, 250 mg qd Toenails	3		14/48	(69%)	37/45
Van der Schroeff et al. (1992), ref. 25					6 mo
Terbinafine, 250 mg qd	1.5		6/9		9/9
Terbinafine, 250 mg qd	3		4/7		7/9
Terbinafine, 250 mg qd Fingernails	6		3/6		7/9
Terbinafine, 250 mg qd	1.5		11/30		18/30
Terbinafine, 250 mg qd	3		12/33		28/34
Terbinafine, 250 mg qd Toenails	6		15/33		27/34
Baudraz-Rosselet et al. (1992), ref. 28					6 mo
Terbinafine, 250 mg qd Fingernails	6		(100%)		(86%)
Terbinafine, 250 mg qd Toenails	6	(46%)	(77%)		(91%)
Villars and Jones (1992), ref. 26					12 mo
Terbinafine, 250 mg qd Fingernails	1.5	(95%)	(95%)		
Terbinafine, 250 mg qd Toenails	1.5–3	(40–70%)	(40–70%)		(12–18% recurrence)

many were being treated for multiple medical problems (15).

Itraconazole

Like fluconazole, itraconazole has been used successfully to treat several fungal infections. More recently, it has been investigated for the treatment of onychomycosis. Using mainly 100 mg daily for a period ranging from 3 to 12 months of treatment (Table 1) results in an overall cure rate in fingernails ranging from 64 to 100% with a recurrence rate of 0 to 17% after 6 months follow-up. In toenails, clinical cure rates have varied widely, ranging from 0 to 92% of patients, and mycologic cure was shown in 3 to 73% with a recurrence rate of 0 to 11%. Once again, the significance of these latter results varies according to study design, sample size, duration of treatment, and length of follow-up. For instance, Hanifin and Tofte (16) in 1988, were unable to cure any of four patients treated for 3 to 6 months with itraconazole for toenail onychomycosis, but patients were not followed up after treatment was stopped.

Walsoe et al. (17) in 1990, treated 34 patients of which only one was cured clinically and mycologically after receiving itraconazole for 6 to 8 months, as compared with 0 of 10 cured after receiving griseofulvin for 6 months at 500 mg daily. A similar study by Arenas et al. (18), in 1991, however, had a 92% clinical cure rate of 12 patients with itraconazole versus 33% of 15 cured on griseofulvin. In this study, patients were excluded from the data if their infected toenail did not improve after 3 months of therapy. Two of the patients receiving itraconazole and none receiving griseofulvin were apparently eliminated from the study for this reason, thus accounting for the relatively higher reported cure rate with itraconazole.

Although several studies could not prove the superior efficacy of itraconazole over griseofulvin, the newer drug seemed to be much better tolerated. Korting et al. (5) found no significant difference in toenail cure rates between itraconazole and high-dose ultramicrosize griseofulvin (990 mg daily), although a significantly lower incidence of side effects such as headache, nausea, and diarrhea were noted in patients receiving itraconazole as compared with griseofulvin.

One encouraging study on itraconazole was reported by Willemsen et al. (19) who treated patients for only 3 months with either 100 or 200 mg daily of the drug. Both doses cured 100% of infected fingernails, and all patients remained cured after 6 months follow-up. In those with infected toenails, 13% and 19% were mycologically cured receiving 100 and 200 mg daily dosage, respectively. However, after 6 months follow-up, these cure rates rose sharply to 26% and 79%, respectively (47% and 58% clinically cured). This was explained by the remarkable bioavailability of itraconazole, because Willemsen et al. (19) found high concentrations of the drug in the distal nail plate after only 3 months of treatment, remaining at high levels up to 6 months after treatment was stopped.

More recent reports have dealt with pulse therapy with monthly cycles of 400 mg itraconazole daily for 1 week over 3 to 4 months. In an open study, De Doncker et al. (20), used this regimen on 50 patients with toenail onychomycosis. After a mean follow-up period of 1 year, 80% of these patients were clinically cured, whereas 72% and 80% had a negative KOH and fungal culture, respectively.

The incidence of hepatic reactions has been reported as approximately 6 in 5 million patients, with the most common side effects being limited to gastrointestinal complaints (5%), headache (1.5%), dizziness (1%), rash (1%), and pruritus (1%) (21).

Terbinafine

Consistently greater cure rates that include follow-up have recently been reported in medical literature with terbinafine than with itraconazole (Table 1). This allylamine is fungicidal rather than fungistatic, inhibiting squalene epoxidase, a vital enzyme for the production of ergosterol in the fungal cell membrane (22). It is believed that the accumulation of squalene is toxic to the fungus and causes cell death.

Terbinafine in its topical (cream) form has already been approved for the treatment of fungal infections of the skin, such as tinea pedis and tinea corporis. Studies of a 1-week trial of terbinafine 1% cream for tinea pedis resulted in mycologic cure in 88% of patients up to 5 weeks after treatment (23). This compares favorably with the 38% mycologic cure reported with a 1-week course of clotrimazole (24). Adequate response with clotrimazole typically requires up to 4 weeks of treatment, and recurrences are common.

Studies using 250 mg daily of terbinafine over a treatment period of 1.5 to 6 months have shown 71 to 100% clinical and 50 to 100% mycologic cure rates for fingernail onychomycosis. The lowest mycologic cure rate (50%) found by Van der Schroeff et al. (25), in 1992, even improved to 78% in 6 months of follow-up after treatment was stopped. Villars and Jones (26), in 1992, had much larger sample sizes than the other studies (*n* = 96), and found a 95% cure rate after only 6 weeks of treatment.

Toenail onychomycosis treated with terbinafine had clinical cure rates ranging from 40% in 6 weeks, to 70% in 3 months, to 88% in 12 months of treatment (26, 27). Mycologic cure was most impressive when patients were followed up after treatment. Table 1 shows that mycologic cure rates rose sharply when patients receiving 1.5 to 6 months of terbinafine were followed 6–9 months later. For example, Goodfield et al. (22) in 1992, found a 29% mycologic cure rate at the end of a 3-month course of treatment with terbinafine. This percentage increased to 82% when the study subjects were followed for 6 months after treatment was discontinued. Van der Schroeff et al. for 6 months (25), in 1992, discovered that a short course of 6 weeks of terbinafine mycologically cured 37% of the patients; however, up to 60% were cured after a 6-month follow-up. The highest overall cure rate was reported by Baudraz-Rosselet et al. (28), in 1992, whereas the cure rate rose from 77% to 91% after a treatment course of up to 6 months was followed for an additional 6 months. These long-term findings are consistent with the 100% mycologic cure in patients studied by Goodfield et al (27), in 1989, who were on 12 months of terbinafine.

As with itraconazole, it appears that even short courses of terbinafine can be effective in sufficiently penetrating the nail and remaining there in therapeutic concentrations long after treatment is stopped. Documented recurrence rates are low, comparing very favorably with the reported 60% recurrence rate with griseofulvin shown by Kaden's study (3). Villars and Jones (26), in 1992, found an 18% recurrence of toenail onychomycosis up to 12 months after a 6-week course of treatment, and a 12% recurrence after a 12-week course of treatment.

Adverse effects in studies with terbinafine were limited mainly to mild gastrointestinal symptoms, skin reactions, and headache. Average percentages of these symptoms were well represented in the study of 117 patients by Van der Schroeff et al. (25); 16%, 7%, and 4%, respectively. Even lower occurrences of minor side effects were reported by Villars and Jones (29), in 1989, 5.8% overall and 3.5% related to the gastrointestinal tract of a total of 452 patients receiving terbinafine. The superiority of terbinafine in onychomycosis therapy was best summarized in a recent meta-analysis by Einarson et al. (30) comparing the cost-effectiveness of terbinafine, griseofulvin, and ketoconazole. This study showed terbinafine to have the shortest duration of treatment (3 to 4 months), highest cure rate (95% fingernails, 78% toenails), and lowest relapse rate of the three drugs.

It is clear that griseofulvin and ketoconazole are being used less in the treatment of onychomycosis now with the introduction of fluconazole, itraconazole, and terbinafine, all of which are safe and more effective. Griseofulvin seems to enter the nail plate from the lunula, hence its effect can only be as fast as the nail grows. On the other hand, the rapid penetration of nails by both itraconazole and terbinafine show that these drugs can also directly enter the nail plate via the nail bed (19).

Terbinafine has already been used in Europe and Canada to treat fungal nail infections and has recently been approved in the United States in oral form. Itraconazole has recently been approved as well, but fluconazole is not yet approved for onychomycosis in the United States. It would be useful to compare the three drugs directly in well-controlled studies of onychomycosis treatment. Is the fungicidal mechanism of action of terbinafine superior to the fungistatic properties of itraconazole and fluconazole?

One report did directly compare terbinafine to itraconazole for toenail onychomycosis. Brautigam et al. (31) equally and randomly divided 195 patients with toenail onychomycosis into two groups taking in a double-blind fashion either 250 mg daily of terbinafine or 200 mg daily of itraconazole for 12 weeks with a 40-week follow-up. At the end of the study, 81% (70/86) of the patients receiving terbinafine were cured mycologically, whereas 63% (53/84) of the patients receiving itraconazole had such a cure. Clinical improvement was also significantly greater in the terbinafine group than in the itraconazole group.

Some attempt has been made to claim superiority of the triazoles over terbinafine because they cover a broader spectrum of organisms. For example, they are more effective against yeasts, *in vitro,* than terbinafine. Recent reports of the increasing incidence of positive nail cultures for yeasts have fueled the argument for using broad-spectrum antifungals, although yeasts are not usually considered primary pathogens (32). The predominance of dermatophytes, which are always considered pathogenic, in onychomycosis should not be overlooked. The drugs that most effectively treat dermatophytes are likely to be most effective against onychomycosis. One study of more than 2,000 fungal nail isolates found cultures positive for the same three dermatophytes in 91%, whereas *Candida albicans* grew in 5.4% of these isolates (33). Nondermatophytes, particularly *Scopulariopsis brevicaulis, Hendersonula toruloidea,* and *Aspergillus sydowii,* made up 2.8% of the positive fungal cultures.

An investigation is currently underway to differentiate the efficacy of terbinafine against various types of fungi. Minimum inhibitory concentrations (MICs) (*in vitro*) of terbinafine appear to be much lower for dermatophytes (such as *T. rubrum*) than for Candida species. Clayton (34) reported an MIC range for dermatophytes as 1 to 60 ng/mL, whereas in *C. parapsilosis* and *C. albicans,* MICs ranged from 130 to 3,130 ng/ml and 6,250 to greater than 128,000 ng/ml, respectively. This 100 to 1,000-fold difference between the types of fungi commonly found in nails may be related to the pharmacokinetic studies of terbinafine by Finlay (35). The steady-state concentration of terbinafine found in the most distal portion of nails ranged from 250 to 550 ng/g. Such levels are well above the MICs for dermatophytes, but not adequate in meeting the MICs of the *Candida* species.

In a report by Meinhof (36), itraconazole overall had a 100-fold lower MIC against yeasts than terbinafine, but a similar MIC for dermatophytes. Results of *in vitro* testing of fluconazole have been inconsistent with the drug's clinical efficacy. For example, the MIC for *C. albicans* ranges from 0.125 to greater than 100 ng/mL, whereas with the clinically less effective ketoconazole the MIC ranges from less than 0.0015 to 12.5 ng/mL (14).

In vitro data cannot be used to predict clinical outcomes. With newer drugs available, older treatments for onychomycosis are being replaced rapidly. In the countries in which it is approved for onychomycosis, terbinafine has become the first line of therapy. Terbinafine, itraconazole, and fluconazole all offer substantial advantages over griseofulvin, and it is likely that the use of these drugs for onychomycosis will result in faster, longer lasting responses and higher cure rates.

References

1. Samman PD, Fenton DA, editors. The nails in disease. 2nd ed. Chicago: Yearbook Medical Publishers; 1986, p. 6.
2. Malawista SE, Sato H, Bensch KG. Vinblastine and griseofulvin reversibly disrupt the living mitotic spindle. Science 1968; 160:770–772.
3. Kaden R. Klinische und mykologische Nachuntersuchungen griseofulvinbehandelter Onychomykosen. Mycopathologia 1964; 25:351–360.
4. Davies RR, Everall JD, Hamilton E. Mycological and clinical evaluation of griseofulvin for chronic onychomycosis. Br Med J 1967; 3:464–468.
5. Korting HC, Schafer-Korting M, Zienicke H, et al. Treatment of tinea unguium with medium and high doses of ultramicrosize griseofulvin compared with that with itraconazole. Antimicrob Agents Chemother 1993; 37(10):2064–2068.
6. Robertson MH, Rich P, Parker F, Hanifin JM. Ketoconazole in griseofulvin-resistant dermatophytosis. J Am Acad Dermatol 1982; 6:224–229.
7. Galimberti R, Negroni R, Iglesia de Elias Costa MR, Casala AM. The activity of ketoconazole in the treatment of onychomycosis. Rev Infect Dis 1980; 2:596–598.
8. Knight TE, Shikuma CY, Knight J. Ketoconazole induced fulminant hepatitis necessitating liver transplantation. J Am Acad Dermatol 1991; 251:398–400.
9. Stricker BA, Black APR, Bronkhorst FB, et al. Ketoconazole associated hepatic injury. J Hepatol 1986; 3:399–406.
10. Saag MS, Dismukes WE. Azole antifungal agents: emphasis on new triazoles. Antimicrob Agents Chemother 1988; 32:1–8.
11. Coldiron B. Recalcitrant onychomycosis of the toenails successfully treated with fluconazole. Arch Dermatol 1992; 128:909–910.
12. Kuokkanen K, Alava S. Fluconazole in the treatment of onychomycosis caused by dermatophytes. J Dermatol Treat 1992; 3:115–117.
13. Smith SW, Sealy DP, Schneider E, Lackland D. An evaluation of the safety and efficacy of fluconazole in the treatment of onychomycosis. South Med J 1995; 88(12): 1217–1220.
14. Grant SM, Clissold SP. Fluconazole: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial and systemic mycoses. Drugs 1990; 39:877–917.
15. Hay RJ. Risk/benefit ratio of modern antifungal therapy: Focus on hepatic reactions. J Am Acad Dermatol 1993; 29(1):S50–S54.
16. Hanifin JM, Tofte SJ. Itraconazole therapy for recalcitrant dermatophyte infections. J Am Acad Dermatol 1988; 18:1077–1080.
17. Walsoe I, Stangerup M, Svejgaärd E. Itraconazole in onychomycosis: Open and double-blind studies. Acta Derm Venereol 1990; 70:137–140.
18. Arenas R, Fernandez G, Dominguez L. Onychomycosis treated with itraconazole of griseofulvin alone with and without a topical antimycotic or keratolytic agent. Int J Dermatol 1991; 30(8):586–589.
19. Willemsen M, De Doncker P, Willems J, et al. Posttreatment itraconazole levels in the nail: New implications for treatment in onychomycosis. J Am Acad Dermatol 1992; 26:731–735.
20. De Doncker P, Decroix J, Pierard GE, et al. Antifungal pulse therapy for onychomycosis: A pharmacokinetic and pharmacodynamic investigation of monthly cycles of 1-week pulse therapy with itraconazole. Arch Dermatol 1996; 132(1):34–41.
21. Lavrijsen AO, Balmus KJ, Nugteren-Huying WM, et al. Hepatic injury associated with itraconazole. Lancet 1992; 340:251–252.
22. Goodfield MJD, Andrew L, Evans EGV. Short term treatment of dermatophyte onychomycosis with terbinafine. BMJ 1992; 304:1151–1153.
23. Berman B, Ellis C, Leyden J, et al. Efficacy of a 1-week, twice-daily regimen of terbinafine 1% cream in the treatment of interdigital tinea pedis. J Am Acad Dermatol 1992; 26:956–960.
24. Bergstresser PR, Elewski B, Hanifin J, et al. Topical terbinafine and clotrimazole in interdigital tinea pedis: A multicenter comparison of cure and relapse rates with 1- and 4-week treatment regimens. J Am Acad Dermatol 1993; 28:648–651.
25. Van der Schroeff JG, Cirkel PKS, Crijns MB, et al. A randomized treatment duration-finding study of terbinafine in onychomycosis. Br J Dermatol 1992; 126 Suppl 39:36–39.
26. Villars VV, Jones TC. Special features of the clinical use of oral terbinafine in the treatment of fungal diseases. Br J Dermatol 1992; 126 Suppl 39:61–69.
27. Goodfield MJD, Rowell NR, Forster RA, et al. Treatment of dermatophyte infection of the finger- and toe-nails with terbinafine (SF 86-327, Lamisil), an orally active fungicidal agent. Br J Dermatol 1989; 121:753–757.
28. Baudraz-Rosselet F, Rakosi T, Wili PB, Kenzelmann R. Treatment of onychomycosis with terbinafine. Br J Dermatol 1992; 126 Suppl 39:40–46.
29. Villars VV, Jones JC. Clinical efficacy and tolerability of terbinafine (Lamisil)—A new topical and systemic fungicidal drug for treatment of dermatomycoses. Rev Infect Dis 1989; 14:124–127.
30. Einarson TR, Arikian SR, Shear NH. Cost-effectiveness analysis of onychomycosis therapy in Canada from a

government perspective. Br J Dermatol 1994; 130 Suppl 43:32–34.

31. Brautigam M, Nolting S, Schopf RE, Weidinger G. Randomised double blind comparison of terbinafine and itraconazole for treatment of toenail tinea infection. BMJ 1995; 311:919–922.
32. Pierard GE, Arrese JE, De Doncker P, Pierard-Franchimont C. Present and potential diagnostic techniques in onychomycosis. J Am Acad Dermatol 1996; 34(2 Pt 1):273–277.
33. Summerbell RC, Kane J, Krajden S. Onychomycosis, tinea pedis and tinea manuum caused by nondermatophytic filamentous fungi. Mycoses 1989; 32(8): 609–619.
34. Clayton YM. In vitro activity of terbinafine. Clin Exp Dermatol 1989; 14:101–103.
35. Finlay AY. Pharmacokinetics of terbinafine in the nail. Br J Dermatol 1992; 126 Suppl 39:28–32.
36. Meinhof W. Kinetics and spectrum of activity of oral antifungals: the therapeutic implications. J Am Acad Dermatol 1993; 29(1):S37–S41.
37. Nahass GT, Sisto M. Onychomycosis: successful treatment with once-weekly fluconazole. Dermatology 1993; 186:59–61.
38. Hay RJ, Clayton YM, Moore MK, Midgely G. An evaluation of itraconazole in the management of onychomycosis. Br J Dermatol 1988; 119:359–366.

Anemia Secondary to Low Erythropoietin in a Patient with Normal Renal Function

ANDRE M. KALLAB, M.D., GARBIS DABAGHIAN, M.D., AND TERENIG TERJANIAN, M.D.

Abstract

Anemia with a relatively low erythropoietin level has been described in several medical conditions associated with chronic inflammatory diseases such as rheumatoid arthritis, cancer, sickle cell disease, chronic renal failure, acquired immunodeficiency syndrome, and severe autonomic nervous system failure. This case report describes the development of anemia with a relatively low erythropoietin level in a 65-year-old man with non-insulin-dependent diabetes mellitus, normal renal function, and negative hematologic, thyroid, and autoimmune disease work-ups. The serum erythropoietin level was 14 mU/mL (N: 10–20 mU/mL). The hemoglobin was 7.5 g/dL and the hematocrit was 24%. The patient was treated with recombinant erythropoietin at 50 U/kg subcutaneously three times weekly. The hemoglobin level increased over a 4-week period. When erythropoietin was stopped, the anemia recurred in 2 months. We conclude that the patient's anemia was caused by a relative lack of endogenous erythropoietin release. The exact mechanism of this anemia is unknown. We recommend including a test for erythropoietin level in the evaluation of any unexplained anemia. **Key Words:** anemia, erythropoietin, normal renal function, non-insulin-dependent diabetes mellitus

ERYTHROPOIETIN IS A GLYCOPROTEIN GROWTH FACTOR synthesized by the kidney (1) and probably the liver (2–4) in response to hypoxia. Anemia with low erythropoietin levels has been described in several medical conditions such as chronic inflammatory diseases, cancer, sickle cell anemia, chronic renal failure, acquired immunodeficiency syndrome, and autonomic nervous system failure. Low erythropoietin levels also have been reported in six anemic, insulin-dependent diabetic patients with normal renal function (5). This case report describes an anemic, nonuremic, non-insulin-dependent diabetic patient with a low erythropoietin level, who responded to replacement therapy with erythropoietin.

Case Report

The patient was a 65-year-old man with a past medical history of seizure disorder, normal pressure hydrocephalus with a ventriculoperitoneal shunt, non-insulin-dependent diabetes mellitus (NIDDM), and chronic anemia for 2 years. There was no history of smoking or alcohol abuse. The patient was first referred to the hematology service for evaluation in August 1993. He denied any pain, fever, nausea, vomiting, cough, night sweats, joint pain or swelling, significant weight loss, or poor appetite. There was no history of decreased sweating, impaired gastric emptying, impotence, or other features of autonomic dysfunction. His medications included glyburide, perphenazine, and phenytoin.

On physical examination, the vital signs were normal with a supine blood pressure of 110/60 mm Hg and a standing blood pressure of 105/55 mm Hg. Examination of the head and neck revealed pale conjunctivae, normal fundi, nonicteric

---

From the Department of Internal Medicine, Division of Hematology, Staten Island University Hospital, Staten Island, New York. Address correspondence to Garbis Dabaghian, MD, Staten Island University Hospital, 475 Seaview Ave., Staten Island, NY 10305.

sclerae, and a normally papillated tongue. The lungs were clear to auscultation and the heart sounds were normal. The abdomen was soft without evidence of hepatosplenomegaly or palpable mass. The extremities were neither cyanotic nor edematous, and no digital clubbing was noted. A stool specimen for occult blood was negative. The neurological examination revealed a mildly demented patient with gait disturbance and without any signs of autonomic dysfunction. Six years before the evaluation of the patient's anemia, his laboratory analysis revealed a hemoglobin of 14.6 g/dL and a hematocrit of 41.3%. Three years later, a gradual decrease in hemoglobin and hematocrit was noted. By the time he was seen by the hematologist, his hemoglobin and hematocrit levels were 7.5 g/dL and 22%, respectively, with a normal mean corpuscular volume. Table 1 lists some relevant hematological and blood tests. A liver-spleen computed tomographic scan was unremarkable. The bone marrow aspirate was nondiagnostic, and the chromosomal analysis revealed a 46,XY pattern. The patient was treated with erythropoietin at 50 U/kg subcutaneously three times weekly, and his anemia improved in 4 weeks (hemoglobin, 11.3 g/dL; hematocrit, 34.6%). Erythropoietin was continued until the hemoglobin stabilized at 13 g/dL, and it was then tapered and discontinued. Two months after discontinuing erythropoietin, the hemoglobin and hematocrit decreased to 7.6 g/dL and 21.8%, respectively. At that time, the erythropoietin plasma level was 13 mU/mL. Again, therapy with erythropoietin corrected the anemia. A sedimentation rate obtained after the anemia was corrected was 2 mm/hr.

TABLE 1

Hematological and Blood Chemical Values of the Patient at Evaluation and 4 Weeks after Erythropoietin Therapy

	At Evaluation	4 Weeks Later	Normal Range
Hgb (g/dL)	7.5	11.3	14–18
Hct (%)	22	34.6	42–52
MCV (fL)	90		80–94
BUN (mg/dL)	12		10–26
Serum creatinine (mg/dL)	0.6		0.2–1.5
Creatinine clearance (mL/min)	90		85–125
Vitamin B_{12} (pg/mL)	871		199–732
Folate (ng/mL)	17.5		2.8–13.5
Serum iron (µg/dL)	66		35–150
Iron binding capacity (µg/dL)	187		200–400
Ferritin (ng/mL)	180		14–179
Serum erythropoeitin (mU/mL)	14		0–27

Urinalysis, serum electrolytes, liver function tests, thyroid function tests, rheumatoid factor, antinuclear antibody, and serum protein electrophoresis were within normal levels. Hgb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; BUN, blood urea nitrogen.

Discussion

Erythropoietin is a glycoprotein growth factor synthesized by cells in the kidney in response to signals from a renal oxygen-sensing device, probably a heme protein (1). Small amounts of erythropoietin and its messenger RNA have also been isolated from the liver (2–4). In the bone marrow, erythropoietin binds to and activates specific receptors on the erythroid progenitor cells (6). In the presence of this erythropoietin-receptor complex, the progenitor cells continue their predestined development into mature erythrocytes (1). In its absence, they disintegrate and die (7). Erythropoietin plasma titers, as measured by radioimmunoassays and bioimmunoassays, bear a logarithmic relationship to hemoglobin concentration or hematocrit (8). The range of this relationship is broad, reflecting both the crude bioassay technique and the effect of cardiac output, redistribution of blood, hemoglobin-oxygen affinity, and other compensatory factors called into action in individuals with anemia (9). Under normal steady state conditions, 10 to 20 units of erythropoietin per liter of plasma induces the production of enough erythrocytes to maintain the delivery of oxygen to the renal oxygen sensor sufficient (1). In severe anemia, the reduced delivery of oxygen increases the rate of renal cell erythropoietin synthesis exponentially (8).

Plasma titers of erythropoietin are lower in patients with renal failure than in nonuremic patients with anemia (10, 11). However, it has also been suggested that erythropoietin production is suboptimal in many other conditions such as rheumatoid arthritis (12–14), sickle cell anemia (15), severe autonomic failure (16), HIV-infected patients being treated with zidovudine (17–19), and the anemia of cancer in which the blunted erythropoietin level worsens with chemotherapy (20–22). The pathophysiology of the decreased erythropoietin production in these conditions is poorly understood, probably multifactorial, and could be caused by the production of certain factors (interleukin-1, tumor necrosis factor, and γ-interferon). Anemia in patients with diabetes mellitus is usually caused by inflammatory illness or renal insufficiency. However, a unique form of anemia in insulin-dependent diabetics with normal serum creatinine but inappropriately low erythropoietin response has been described in six patients (5).

Our patient is a non-insulin-dependent diabetic, with normal pressure hydrocephalus, who developed a progressive symptomatic, normochromic, normocytic anemia with an inappropriate endogenous erythropoietin release. The patient did not have any evidence of kidney failure, rheumatoid arthritis (or other chronic inflammatory disease), sickle cell disease, obvious malignancy, acquired immunodeficiency syndrome or autonomic failure. He was treated with recombinant erythropoietin subcutaneously at a relatively low dose (50 U/kg, three times weekly), and within 4 weeks his hematocrit increased from 22 to 34.6%. When the erythropoietin injections were discontinued, the anemia recurred. We conclude that the patient's anemia was caused by either inadequate endogenous erythropoietin production or release, the exact mechanism being unknown. Although diabetes mellitus may play a role (5), especially with renal involvement, the plasma level of erythropoietin may not be a factor at all because its level may be elevated in diabetic patients (23).

Based on the experience with this patient, it is difficult to conclude whether the problem is caused by primary congenital or acquired primary hypoerythropoietinemia, or that there is, as yet, an undetected underlying disease. Thus, we recommend including a test for erythropoietin level in the work-up of any unexplained and otherwise unresponsive anemia. Further investigation is warranted to identify causes of inadequate levels of erythropoietin.

References

1. Erslev AJ. Erythropoietin. N Engl J Med 1991; 324:1339–1344.
2. Jacobs K, Shoemaker C, Rudersdorf R, et al. Isolation and characterization of genomic and c DNA clones of human erythropoietin. Nature 1985; 313:806–810.
3. Bondurant MC, Koury MJ. Anemia induces accumulation of erythropoietin mRNA in the kidney and liver. Mol Cell Biol 1986; 6:2731–2733.
4. Fried W. The liver as a source of extrarenal erythropoietin. Blood 1972; 40:671–677.
5. Rarick MU, Espina BM, Colley D, et al. Treatment of a unique anemia in patients with insulin-dependent diabetes mellitus with epoietin-alpha [Abstract]. Blood 1993; 82(10) suppl 1:354.
6. Sawyer ST, Krantz SB, Sawada K. Receptors for erythropoietin in mouse and human erythroid cells and placenta. Blood 1989; 74:103–109.
7. Koury MJ, Bondurant MC. Erythropoietin retards DNA breakdown and prevents programmed death in erythroid progenitor cells. Science 1990; 248:378–381.
8. Erslev AJ, Caro J, Miller O, Silver R. Plasma erythropoietin in health and disease. Ann Clin Lab Sci 1980; 10: 250–257.
9. Erslev AJ, Wilson J, Caro J. Erythropoietin titers in anemic, nonuremic patients. J Lab Clin Med 1987; 109: 429–433.
10. Radtke HW, Claussner A, Erbes PM, et al. Serum erythropoietin concentration in chronic renal failure: Relationship to degree of anemia and excretory renal function. Blood 1979; 54:877–884.
11. Caro J, Brown S, Miller O, et al. Erythropoietin levels in uremic nephric and anephric patients. J Lab Clin Med 1979; 93:449–458.
12. Pavlovic-Kentora V, Ruvidic R, Milenkovic P, Marinkovic D. Erythropoietin in patients with anemia in rheumatoid arthritis. Scand J Haematol 1979; 23:141–145.
13. Baer AN, Dessypris EN, Goldwasser E, Krantz SB. Blunted erythropoietin response to anemia in rheumatoid arthritis. Br J Haematol 1987; 66:559–564.
14. Cavill I, Bentley DP. Erythropoiesis in the anemia of rheumatoid arthritis. Br J Haematol 1982; 50:583–590.
15. Sherwood JB, Goldwasser E, Chilcote R, et al. Sickle cell anemia patients have low erythropoietin levels for their degree of anemia. Blood 1986; 67:46–49.
16. Biaggioni I, Robertson D, Krantz S, et al. The anemia of primary autonomic failure and its reversal with recombinant erythropoietin. Ann Intern Med 1994; 121:181–186.
17. Spivak JL, Barnes DC, Fuchs E, Quinn TC. Serum immunoreactive erythropoioetin in HIV infected patients. JAMA 1989; 261:3104–3107.
18. Zon LT, Arkin C, Groopman JE. Haematologic manifestations of the human immune deficiency virus (HIV). Br J Haematol 1987; 66:251–256.
19. Spivak JL, Bender BS, Quinn TC. Hematologic abnormalities in the acquired immune deficiency syndrome. Am J Med 1984; 77:224–228.
20. Miller CB, Jones RJ, Piantadosi S, et al. Decreased erythropoietin response in patients with the anemia of cancer. N Engl J Med 1990; 332:1689–1692.
21. Dainiak N, Kulkarni V, Howard D, et al. Mechanisms of abnormal erythropoiesis in malignancy. Cancer 1983; 51:1101–1106.
22. Cox R, Musial T, Gyde OHB. Reduced erythropoietin levels as a cause of anemia in patients with lung cancer. Eur J Cancer Clin Oncol 1986; 22:511–514.
23. Grzeszczak W, Franek E, Kokot F. Plasma erythropoietin level in patients with diabetes mellitus type II. Pol Arch Med Wewn 1992; 88:18–24.

Screening for Lyme Disease in Hospitalized Psychiatric Patients:

Prospective Serosurvey in an Endemic Area

Robert B. Nadelman, M.D., Edward Herman, M.D.,[1] and Gary P. Wormser, M.D.

Abstract

Background: Nervous system involvement in Lyme disease may mimic certain psychiatric disorders. We studied whether it is worthwhile to conduct routine screening of psychiatric inpatients for serologic evidence of Lyme disease.

Methods: Between March 1988 and June 1989, we prospectively screened sera for Lyme disease from adults admitted to an acute care psychiatric hospital in Westchester County. New York, an area in which this infection is endemic. Of all cases of Lyme disease reported to the U.S. Public Health Service in 1988, 16% originated in Westchester County. The prevalence in healthy blood donors from this area were reported to be 0.7%. Sera were tested by fluorescent immunoassay alone (90%) or fluorescent immunoassay plus enzyme-linked immunosorbent assay (10%).

Results: Sera from only 1 of 517 patients demonstrated antibodies to *Borrelia burgdorferi,* the etiologic agent of Lyme disease (0.2% [95% CI, 0.0% to 1.1%]). This patient had a nonreactive Western blot, which suggested a false-positive antibody test.

Conclusions: We cannot presently recommend routine serologic screening for Lyme disease for adult psychiatric inpatients, even in areas of the United States where this illness is endemic. **Key Words:** Lyme disease, *Borrelia burgdorferi,* Lyme disease, screening

Lyme disease is a multisystem disorder caused by the spirochete *Borrelia burgdorferi,* which is transmitted by the bite of an *Ixodes* tick. Although most patients respond well to treatment, approximately 15–20% of untreated patients and a smaller proportion of treated patients will develop a variety of neurologic manifestations involving the peripheral and/or central nervous system (i.e., neuroborreliosis) (1–3). Among the latter complications is a chronic encephalopathy, characterized by memory, sleep, and mood disorders (1–3). Some patients with neuroborreliosis have had clinical presentations which mimicked certain psychiatric disorders including schizophrenia with and without catatonia, depression, and anorexia nervosa (1–5). It is important to recognize such manifestations of Lyme disease, because most patients with Lyme disease having

---

From the Department of Medicine, Division of Infectious Diseases, and the [1]Department of Psychiatry, New York Medical College, Valhalla, New York. Address correspondence to Robert B. Nadelman, M.D., Westchester County Medical Center, Division of Infectious Diseases, Macy Pavilion 209 Southeast, Valhalla, NY 10595.

Presented, in part, at the IVth International Conference on Lyme Borreliosis, Stockholm, Sweden, June 18–21, 1990.

The study was partly funded by a grant from the New York State Department of Health. Drs. Nadelman and Wormser are supported in part by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (RO1-AR41508), and from the Centers for Disease Control and Prevention (CDC) (Cooperative Agreements U50/CCU 210286-01 [RBN] and U50/CCU 21280-01 [GPW]). Dr. Nadelman also was supported in part by a grant from the New York State Department of Health, Tick-Borne Disease Institute (C-011001). The contents of this report are solely the responsibility of the authors, and do not necessarily represent the official views of any of the above agencies.

cognitive or neuropsychiatric manifestations have been cured or improved by appropriate antimicrobial therapy (1–5).

The broad range of illness caused by *B. burgdorferi* has frequently been compared with the spectrum of disease caused by *Treponema pallidum,* the etiologic spirochetal agent of syphilis. Because patients with neurosyphilis may be misdiagnosed with psychiatric disorders, routine screening for syphilis has been common in psychiatric inpatient units for some time (6), although the cost effectiveness of this policy has been questioned (7).

Because of the parallels between neuroborreliosis and neurosyphilis, we chose to study prospectively the value of serologic screening for Lyme disease in a hospitalized psychiatric patient population in an area in which this infection is endemic.

Methods

Setting

The Westchester County Psychiatric Institute is an acute care public hospital with 63 of its 133 beds devoted to adult admissions (i.e., excluding pediatric/adolescent, detoxification, and forensic units). The catchment area for the Psychiatric Institute includes all of Westchester County, New York, which is located directly north of New York City. In 1988, 741 (16%) of all cases of Lyme disease reported to the United States Public Health Service originated in Westchester County (8, 9). Based on a study of 4,751 healthy blood donors in Westchester County, the seroprevalence rate of antibodies to *B. burgdorferi* has been estimated to be 0.7%, as determined by enzyme-linked immunosorbent assay (ELISA) (10).

Patients

Between March 1988 and June 1989, an attempt was made to obtain serum and clinical data on all adult Westchester County Psychiatric Institute admissions, with the exception of those patients admitted for drug or alcohol detoxification. Patients admitted on more than one occasion were evaluated only at the first admission. Information regarding psychiatric history was reviewed from the chart by one of us, an attending psychiatrist (EH). Diagnoses were classified according to the Diagnostic and Statistical Manual of Mental Disorders (11). Demographic information was also obtained, including patient age, gender, race, and zip code of residence.

Serology

Sera were tested for antibodies to *B. burgdorferi* by fluorescent immunoassay (FIAX®) (Bio Whittaker, Walkersville, MD), a modification of the indirect fluorescent immunoassay (12). Approximately 10% of sera were also tested by ELISA.

Statistics

Statistical comparisons were performed using either the Fisher's exact test or the Student's *t*-test, both two-tailed. A p value equal to or less than 0.05 was considered to indicate statistical significance.

Results

A total of 858 patients meeting study criteria were admitted to the Westchester County Psychiatric Institute during the study, including 476 men (55%) and 355 women (41%) (gender was not recorded for the remaining 27 [3%]). Of the 858 eligible patients, serum was obtained for 517 (60%). Of the 517 sera studied, only one tested positive for antibody to *B. burgdorferi* by FIAX® (0.2%; upper boundary of the 95% CI = 1.1%). To verify the accuracy of the FIAX® results, approximately 10% of sera were re-assayed by ELISA, and also tested negative. The one positive serum sample by FIAX® was obtained from a 26-year-old man admitted with atypical psychosis (discharge diagnosis was dysthymic disorder). Because immunoblotting performed on this serum sample was nonreactive for antibodies specific to Borrelial proteins, the patient was considered to have a false-positive antibody test for Lyme disease. The rapid plasma reagin assay for syphilis was also negative on this serum sample.

Of the 517 patients with sera, clinical information was available for 378 (73%); this group was henceforth referred to as the study group. Patient characteristics are summarized in Table 1. At least 129 patients (34%) resided in those areas of Westchester County and vicinity in which Lyme disease was most prevalent. The primary psychiatric admitting diagnosis for the 378 study group patients is shown in Table 2.

To control for selection bias, demographic characteristics for the 378 study subjects were compared with those for 157 (46%) patients randomly selected from the 341 patients for whom no sera were available. There were no significant differences between these groups with respect to gender, race, age, and frequently and type of psychiatric diagnosis.

TABLE 1

Demographic Information

	Study Group[a] (n = 378)
Men	216 (57%)
Women	162 (43%)
White	233 (62%)
Black	124 (33%)
Other	21 (6%)
Mean age in years (range)	35 (18–85)

[a] Patients with clinical information and serum.

TABLE 2

Primary Psychiatric Diagnosis

	Study Group[a] (n = 378)
Schizophrenia	125 (33%)
Bi-polar disorder	74 (20%)
Depression	47 (12%)
Organic mental disorder	43 (11%)
Psychosis not otherwise classified[b]	38 (10%)
Adjustment disorder[c]	27 (7%)
Other[d]	23 (6%)
Unknown	1 (0.3%)
Prior history of psychiatric illness[e]	295 (78%)

[a] Patients with clinical information and serum.

[b] Includes atypical psychosis, schizoaffective and schizophreniform disorders.

[c] Includes some with depressed mood.

[d] Includes personality, eating, and anxiety disorders.

[e] Range, 1 month to 45 years; median, 6 years; mean, 9.2 ± 8.5 years.

Discussion

Although the Westchester County Psychiatric Institute is located in an area in which Lyme disease is endemic, we were able to detect serologic evidence of Lyme disease in only 1 of 517 adult admissions over 15 consecutive months. Even this single positive sample was believed to have been a false positive on the basis of immunoblotting. We therefore believe that unsuspected Lyme disease is a rare cause for psychiatric admission at our Center.

An alternative explanation for our failure to detect seropositivity might have been the use of a serologic test with low sensitivity. However, this seems unlikely. The method we used (FIAX®) has a sensitivity ranging from 62% (13) to 86% (12) for Lyme disease patients symptomatic for more than 2 weeks. In addition, repeat testing of approximately 10% of the serum specimens by a second commonly used method (ELISA) failed to detect any additional seropositive patients. Even if one assumed only a 50% sensitivity for the FIAX® assay, we would have expected only one additional seropositive patient (2 of 517 [0.4%]; 95% CI: 0.05% to 1.4%). In fact, the low rate of seropositivity in our patients (1 of 517 [0.2%]; 95% CI: 0.004% to 1.1%) was approximately the same as that of healthy blood donors in Westchester County (33 of 4,751 donors [0.7%]; 95% CI: 0.5% to 0.9%) (p = 0.25) (10). Neuroborreliosis may occur in the absence of a positive serum antibody test, but this is believed to be a rate occurrence (3). The use of other methods to detect the rare instances of seronegative neuroborreliosis, such as lymphoproliferative assays of peripheral blood mononuclear cells in response to *B. burgdorferi* antigen (1, 2) or testing for intrathecal antibody production (1) or the presence of *B. burgdorferi* nucleic acids in cerebral spinal fluid by polymerase chain reaction, are too cumbersome to be useful as screening measures.

Although we were unable to find serologic evidence of Lyme disease in adult psychiatric inpatients, we cannot draw any conclusions about the incidence of Lyme disease in children or in outpatients. Our findings may also not pertain to Lyme endemic areas in Europe where neuroborreliosis appears to be more common than in the United States (14). In addition, we cannot exclude the possibility that patients with certain psychiatric diagnoses (e.g., those with "organic" dysfunction) may be more likely to have neuroborreliosis than the population which we studied. Finally, it is possible that a more sensitive assay for neuroborreliosis may be developed in the future. In the absence of further data, it seems reasonable to consider the diagnosis of neuroborreliosis in some psychiatric patients, particularly those from an endemic area, whose examination suggests an "organic" component.

Conclusion

Based on our findings, we cannot presently recommend the inclusion of serologic screening for infection with *B. burgdorferi* as part of the routine laboratory testing for adult psychiatric inpatients, even in areas of the United States in which Lyme disease is endemic.

Acknowledgments

We thank Michael Krauss, Lynda Mack, Denise Cooper, Susan Bittker, Gilda Forseter, Teresa Pace-Pouw, Dr. Charles Pavia, and the Psychiatric Institute staff for their valuable assistance in conducting this study, Dr. Jorge Benach for performing serum immunoblotting, and Nina Cerny for her translation of German references.

References

1. Halperin JJ, Luft BJ, Anand AK, et al. Lyme neuroborreliosis: Central nervous system manifestation. Neurology 1989; 39:753–759.

2. Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. N Engl J Med 1990; 323:1438–1444.
3. Pachner AR. Spirochetal diseases of the CNS. Neurol Clin 1986; 4:207–222.
4. Neumärker KJ, Dudeck U, Plaza P. Borrelien-enzephalitis und Katatonie im Jugendalter. Nervenarzt 1989; 60: 115–119.
5. Roelcke U, Barnett W, Wilder-Smith E, et al. Untreated neuroborreliosis: Bannwarth's syndrome evolving into acute schizophrenic-like psychosis. A case report. J Neurol 1992; 239:129–131.
6. Roberts MC, Emsley RA, Jordaan GP. Screening for syphilis and neurosyphilis in acute psychiatric admissions. S Afr Med J 1992; 82:16–18.
7. Baumgarten A, Swiger ME. A lack of justification for routine screening assays for syphilis in general hospital psychiatric patients. Compr Psychiatry 1987; 28:127–130.
8. Miller GL, Craven RB, Bailey RE, Tsai T. The epidemiology of Lyme disease in the United States 1987–1988. Lab Med 1990; 21:285–289.
9. Bureau of Communicable Disease Control, New York State Department of Health. Surveillance activities, 1988–89.
10. Ciavarella D, Wormser G, Henney C, Aguero-Rosenfeld M. A seroprevalence study of antibodies to *Borrelia burgdorferi* (*Bb*) in blood donors residing in an endemic area [abstract]. Transfusion 1992; 32 8S(Suppl):65S.
11. Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised (DSM-III-R). Washington DC: American Psychiatric Association; 1987.
12. Pennell DR, Wand PJ, Schell RF. Evaluation of quantitative fluorescence immunoassay (FIAX®) for detection of serum antibody to *Borrelia burgdorferi*. J Clin Microbiol 1987; 25:2218–2220.
13. Corpuz M, Hilton E, Lardis MP, et al. Problems in the use of serologic tests for the diagnosis of Lyme disease. Arch Intern Med 1991; 151:1837–1840.
14. Garcia-Monco JG. European Lyme disease. In: Coyle PK, editor. Lyme disease. St. Louis: Mosby, 1993. p. 219–225.

The Imperative to Heal in Traditional Judaism

Fred Rosner, M.D.

In the Jewish tradition, a physician is given specific divine license to practice medicine. Not only is the physician permitted and even obligated to minister to the sick, but the patient is obligated to care for his health and life. Another cardinal principle in Judaism is that human life is of infinite value. The preservation of human life takes precedence over all but three biblical commandments: the prohibitions against idolatry, murder, and forbidden sexual relations such as incest and adultery. To preserve a human life, the Sabbath and even the Day of Atonement may be desecrated, and all other rules and laws (save the above three) are suspended for the overriding consideration of saving a human life.

Judaism never condones the deliberate destruction of human life except in judicial execution for certain criminal acts, in self-defense, or in time of war. Also, you may not sacrifice your life to save another life or even many other lives. Many of the principles of Jewish medical ethics are based on this concept of the infinite value of human life. He who saves one life, asserts the Talmud (Sanhedrin 73a), is as if he saved a whole world. For every person, even a few moments of life are worthwhile.

How far does the physician's obligation to heal extend? Is the physician obligated to endanger his own life to treat patients with contagious and/or communicable diseases? How much risk to his own health and life is the physician allowed or obligated to undertake in the care of his patients? Does the general obligation to visit the sick also include visits to patients with contagious or infectious diseases?

The Physician's Imperative to Heal

The ethical and legal question of whether or not a person is allowed or obligated under Jewish law to become a physician and heal the sick is based on the biblical statement in which God asserts, *I am the Lord that heals you* (Exodus 15:26), which, literally translated from the Hebrew, means "I am the Lord, your physician." If God states that He is the Healer of the sick, how can we, as human physicians, play God, so to speak? The answer is found later in the Bible where the duplicate mention of healing in the phrase and *heal he shall heal* (Exodus 21:19) is interpreted by the Sages of the Talmud (Baba Kamma 85a) to mean that authorization was granted by God to a physician to heal. The Bible implies that it is as if there are two physicians; one is Almighty God, the true Healer of the sick, and the other is the human physician who serves as an instrument of God or an extension of God in the ministrations to the sick.

Many biblical commentators echo this talmudic teaching. By the insistence or emphasis expressed in the double wording *heal he shall heal,* the Bible opposes the erroneous idea that having recourse to medicine shows lack of trust and faith in divine assistance. The Bible takes it for granted that medical therapy is used and actually requires it. Other biblical and rabbinic sources which address the physician's obligation to heal are discussed at length elsewhere (1, 2).

Professor of Medicine, Mount Sinai School of Medicine, New York, New York. Address correspondence to Fred Rosner, M.D., Director, Department of Medicine, Mount Sinai Services at Queens Hospital Center, 82-68 164th Street, Jamaica, NY 11432.

Based on a presentation at a "Conference on Jewish Biomedical Ethics" co-sponsored by Georgetown University and Aish Hatorah, held at Georgetown University Medical Center, Washington, D.C., April 21–23, 1996.

The Patient's Obligation to Seek Healing

A physician is divinely licensed and biblically obligated to heal the sick because of the Jewish concept of the supreme value of human life. Is a patient, however, authorized or perhaps mandated to seek healing from a physician? Is a patient who asks a physician to heal him denying Divine Providence? Is illness an affliction from God that serves as punishment for wrongdoing?

The strongest evidence in Jewish sources that a patient is permitted to seek healing from a physician is found in Maimonides' Code of Jewish Law, known as Mishneh Torah (Deot 3:3) as follows:

> A person should set his heart that his body be healthy and strong in order that his soul be upright to know the Lord. For it is impossible for man to understand and comprehend the wisdoms [of the world] if he is hungry and ailing or if one of his limbs is aching.

Numerous talmudic citations indicate that patients are allowed and even required to seek medical attention. In Jewish tradition, the patient is obligated to care for his health and life. He is charged with preserving his health. He must eat and drink and sustain himself and must seek healing when he is ill in order to be able to serve the Lord in a state of good health. One might arrive at the same conclusion if one were to interpret literally the biblical admonition, *Take therefore good heed unto yourselves* (Deuteronomy 4:15).

The Physician's Obligation to Heal Patients with Contagious Diseases

How far does the physician's divine mandate to heal the sick extend? Is a physician obligated to treat a patient with a contagious disease if there is a risk that he may contract the illness from the patient? Is a physician obligated to endanger his own health or life to restore the health or save the life of the patient?

Jewish law requires that if one sees one's neighbor drowning or being mauled by beasts or attacked by robbers, he is bound to save him (Sanhedrin 73b). This rule is codified by Maimonides (3) and Karo (4). Elsewhere, Karo rules (5) that if one observes a ship sinking with people on board, or a river overflowing its banks, thereby endangering lives, or a pursued person whose life is in danger, one is obligated to desecrate the Sabbath to save the victims. The commentaries of Rabbi Israel Meir Kagan (1838–1933) (6) and Rabbi Abraham Zvi Hirsch Eisenstadt (1813–1868) (7) add that if there is danger involved to the rescuer, the latter is *not* obligated to endanger his life because his life takes precedence over that of his fellow man. If there is only a small risk to the rescuer, he should carefully evaluate the potential danger to himself and act accordingly.

How should a physician proceed if the patient is suffering from a contagious disease? Is the physician allowed to refuse to treat the patient because of the risk or because of his fear of contracting the disease? What if the risk is very small? What is the definition of small risk? If there is a significant risk to the physician of contracting the disease from his patient, Jewish law would certainly agree that the physician would not be obligated to care for that patient. If he wished to care for the patient despite the risk, his act is considered to be a pious act by some writers, and folly by others. If the risk is very remote, however, the physician must care for the patient.

The question as to whether or not a person is obligated or allowed to subject himself to risk in order to save another's life is related to the well-known difference of opinion between the Babylonian and Jerusalem Talmuds. The Jerusalem Talmud (8) posits that a person is obligated to potentially endanger his life if the risk is small to save the life of a fellow human being from certain danger. On the other hand, the Babylonian Talmud (9) voices the opinion that a person is not obligated but is allowed to endanger his life if the risk is small, to save the life of another.

The prevailing opinion among the various rabbinic sources is the one cited by Rabbi David Ibn Zimra (1479–1573) (10). If there is great danger to the rescuer, he is not allowed to attempt to save his fellow man; if he nevertheless does so, he is called a pious fool. If the danger to the rescuer is small and the danger to his fellow man very great, the rescuer is allowed but not obligated to attempt the rescue, and if he does so his act is called an act of loving kindness. If there is no risk at all to the rescuer or if the risk is very small or remote, he is obligated to try to save his fellow man. If he refuses to do so, he is guilty of transgressing the commandment, *thou shalt not stand idly by the blood of thy fellow man* (Leviticus 19:16). This approach is also adopted by recent rabbinic decisors, including Rabbi Moshe Feinstein (11) and Rabbi Eliezer Yehuda Waldenberg (12). Because the risk to physicians and other health care personnel in caring for patients with contagious diseases such as tuberculosis or communicable diseases such as acquired immunodeficiency syndrome (AIDS) is very small if the necessary precautions are taken, a physician is obligated under Jewish law to care for such patients.

Medical history and tradition are replete with examples of physicians whose devotion to their patients transcended their concern for any possible personal danger of contracting their patients' disease. Physicians caring for patients with plague, cholera, typhoid, and polio occasionally became victims themselves. Throughout the ages, the physician's obligations not only to his patients but to society, other health professionals, and to himself have not always been accepted as axiomatic. The profound reluctance of some physicians to care for patients with AIDS prompted Zuger and Miles (13) to review medical responses to other historic plagues. Many physicians, including Galen from Rome in the second century and Sydenham from London in the seventeenth century fled from patients with contagious epidemic diseases. Many of their colleagues, at considerable personal risk, remained behind to care for plague victims.

In Jewish sources, the nearly universal recommendation for those threatened by plague is flight: *He that remains in the city shall die . . . by the pestilence, but he that goes out . . . he shall live* (Jeremiah 21:9–10). The Talmud states that if one finds oneself in a pestilence-ridden town, "gather your feet" (Baba Kamma 60b), which means to flee, or to withdraw to a safe place. During an epidemic of plague, Raba used to close his window shutters (Baba Kamma 60b) because, as Jeremiah (9:20) lamented: *Death is come up unto our windows.*

Jakobovits points out that it was customary in medieval Jewish communities not to assign visitation of plague-stricken patients to anyone except specially appointed persons who were well paid for their perilous work (2). He also cites the seventeenth century records of the Portuguese Congregation in Hamburg, which indicate that even the communal physicians and nurses were exempt from the obligation to attend to infectious patients and that the required services were rendered by volunteers entitled to special remuneration.

The risk of contracting AIDS by examining the patient is extremely small. Hence, Judaism requires physicians and others to care for such patients. Precautions, wherever possible, must be taken by all health care personnel to minimize the chances of sticking or cutting themselves or others with a needle or scalpel which has been used to draw blood from an AIDS patient.

The AMA Council on Ethical and Judicial Affairs stresses doctors' duty to patients with AIDS by stating that: A physician may not ethically refuse to treat a patient whose condition is within the physician's current realm of competence solely because the patient is seropositive. Persons who are seropositive should not be subjected to discrimination based on fear or prejudice. Physicians are dedicated to providing competent medical service with compassion and respect for human dignity. Physicians who are unable to provide the services required by patients with AIDS should make referrals to those physicians or facilities equipped to provide such services.

The American College of Physicians and the Infectious Diseases Society of America believe that physicians, other health care professionals, and hospitals are obligated to provide competent and humane care to all patients, including patients with AIDS and AIDS-related conditions as well as HIV-infected patients with unrelated problems. The denial of appropriate care to patients for any reason is unethical (14). The Association of American Medical Colleges has also adopted a statement concerning the professional responsibility in treating patients with AIDS (15).

The law cannot force people and/or physicians to be courageous or virtuous (16). Moreover, society cannot expect physicians and health care providers to be saints and/or martyrs. The professional obligation of a physician based on the devotion to the moral ideal of healing the sick has some constraints. Physicians are obviously not obligated to treat a patient whose disease and therapy is beyond their competence. Other limiting factors include excessive risk, minimal or questionable benefits, existing obligations to other patients, and competing obligations to family and self (17).

Consensus holds that a person assumes a unique responsibility when he or she enters a healing profession. "Having accepted the mantle of doctor, we are no longer absolutely free to choose which patients we will and will not treat" (18). In this respect, medicine differs from business and most other careers, and therefore, imposes an obligation of effacement of self-interest on the physician. These differences of "the nature of illness, the non-proprietary character of medical knowledge, and the oath of fidelity to the patient's interests generate strong moral obligations." (19)

Conclusion

According to the precepts of Judaism, every human life is infinitely valuable. Therefore, physicians and other health care providers are obligated to endeavor to heal the sick and prolong life. Physicians are not only given divine license to practice medicine; they are also mandated to use their skills to heal the sick. Failing or refusing to do so constitutes a transgression on the part of the physician.

In addition, all people are duty-bound to seek healing from a physician when they are ill and not to rely solely on divine intervention or faith-healing. They are charged with preserving their health when well, and restoring it when ill.

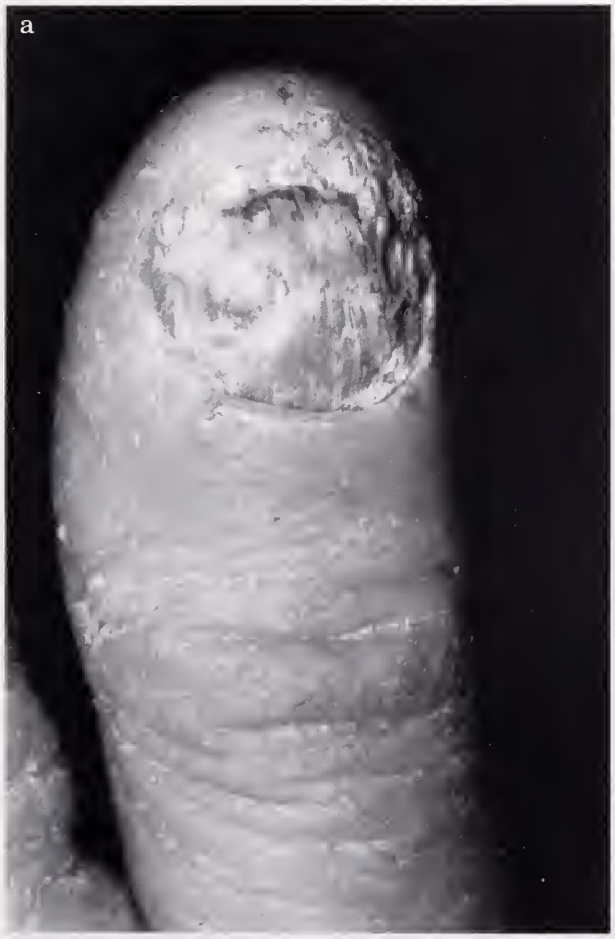
The physician's obligation to heal extends to the care of patients with contagious or communicable diseases if the potential risk to the physician is small. If the risk is substantial, physicians are not obligated to endanger their own lives.

References

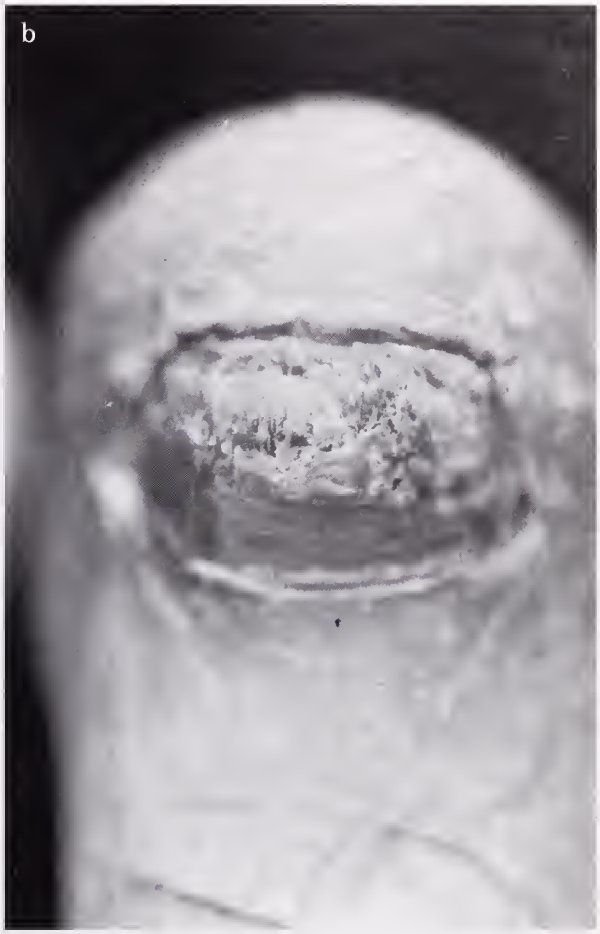
1. Rosner F. Modern medicine and Jewish ethics. 2nd ed. Hoboken (NJ) and New York: Ktav and Yeshiva University Press; 1991.
2. Jakobovits I. Jewish medical ethics. New York: Bloch; 1975.
3. Maimonides M. Mishneh Torah, *Hilchot Rotzeach* 1:14.
4. Karo J. Schulchan Aruch, *Choshen Mishpat* 426:1.
5. Karo J. Schulchan Aruch, *Orach Chayim* 329:8.
6. Kagan IM. Mishnah Berurah 329:19.
7. Eisenstadt AZH. Pitchei Teshuvah, *Choshen Mishpat* 426:2.
8. Terumot. End of Ch 8, according to Ha'Amek Sheelah, She'iltot 147:1.
9. Sanhedrin 73a, according to Agudat Aizov, Derushim folio 3b and Hashmatot folio 38b.
10. Zimra D. Responsa Radvaz, Part 5 (Part 2 in *Leshonot HaRambam,* section 1, 508); Responsa Radvaz 3:627; and Shei'ltot Radvaz 1:52.
11. Feinstein M. Responsa Iggrot Moshe, *Yoreh Deah* Part 2, No. 174:4.
12. Waldenberg EY. Responsa Tzitz Eliezer. Vol. 10 (No. 25):7.
13. Zuger A, Miles SH. Physicians, AIDS, and occupational risk: Historic traditions and ethical obligations. JAMA 1987; 258:1924–1928.
14. Health and Policy Committee, American College of Physicians and the Infectious Diseases Society of America. The acquired immunodeficiency syndrome (AIDS) and infection with the human immunodeficiency virus (HIV). Ann Intern Med 1988; 108:460–469.
15. Professional responsibility in treating AIDS patients: Statement of the Association of American Medical Colleges. J Med Educ 1988; 63:587–590.
16. Annas GJ. Not saints, but healers: The legal duties of health care professionals in the AIDS epidemic. Am J Public Health 1988; 78:844–849.
17. Emmanuel EJ. Do physicians have an obligation to treat patients with AIDS? N Engl J Med 1988; 318:1686–1690.
18. Laskin DM. Treatment of patients with AIDS: A matter of professional ethics. J Oral Maxillofac Surg 1988; 466: 719.
19. Pellegrino ED. Altruism, self-interest, and medical ethics. JAMA 1987; 258:1939–1940.

Dermatology Notes

Onychomycosis vs Psoriasis



a. Onychomycosis of the nail plate.



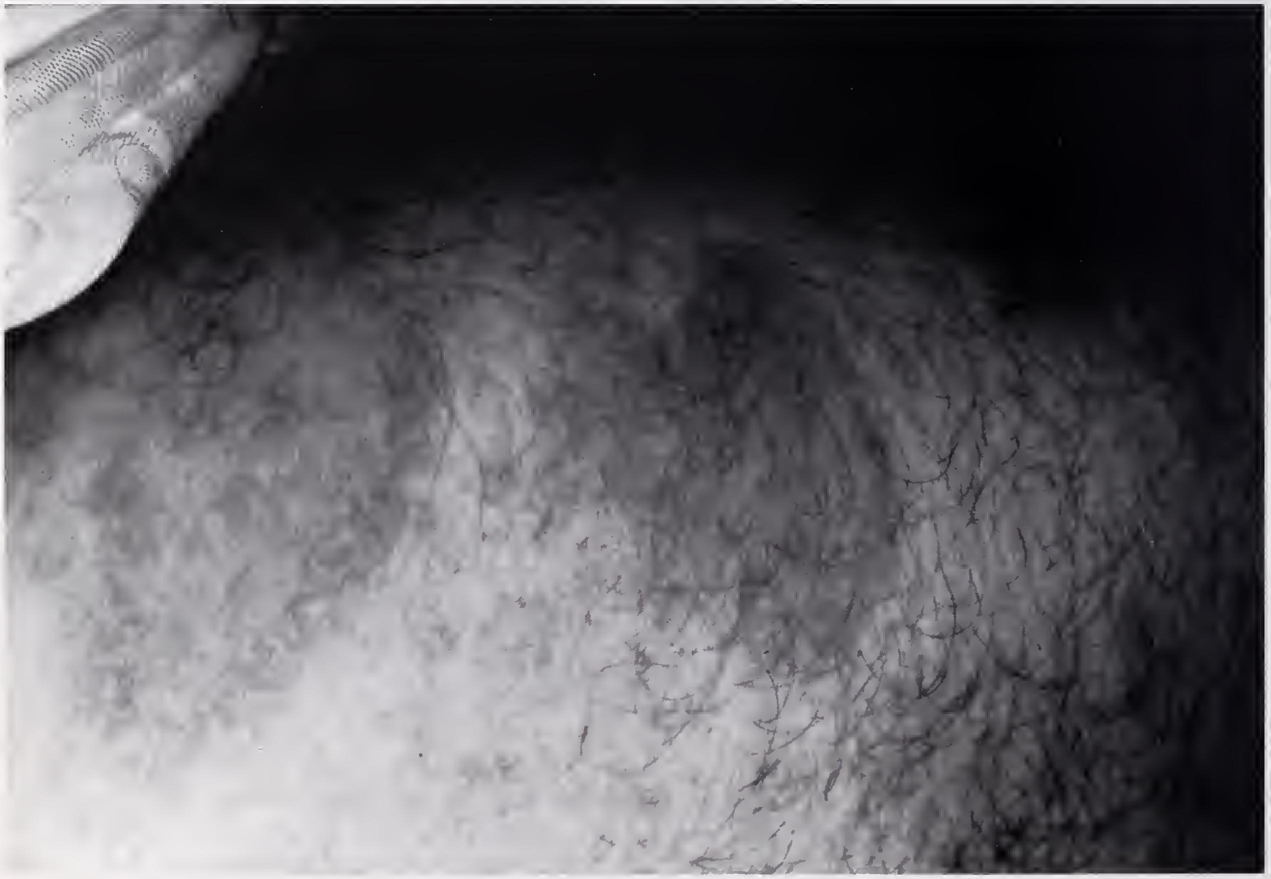
b. Psoriasis of the nail plate.

ONYCHOMYCOSIS OR fungal infection of the nail plate, and psoriasis of the nail may look the same because both conditions may present with hyperkeratosis, discoloration, and onycholysis (separation of the nail plate from the nail bed), as shown here. Other manifestations of psoriasis in nails are pitting, Beau's lines, and the oil drop sign. Beau's lines are horizontal ridges in the nail plate caused by disruption of nail growth in the nail matrix. The oil drop sign indicates round areas of discoloration caused by a combination of dilated blood vessels in the nail bed and onycholysis.

Although psoriasis usually involves extensor surfaces of the skin such as the elbows or knees, the condition may vary greatly in presentation. Well-demarcated, erythematous scaling plaques of psoriasis may occur anywhere on the body including the scalp, genitalia, perianal region, trunk, face, and palms and soles. Occasionally, psoriasis may present only on the nails, resembling onychomycosis. In such a case, clues which favor psoriasis as the diagnosis are diffuse involvement of all 20 nails, a family history of psoriasis in a first-degree relative, dandruff in the scalp, and a negative fungal culture of nail clippings.—*David Hecker, M.D.*

Lyme Disease

ERYTHEMA CHRONICUM migrans is the cutaneous hallmark of Lyme disease. It begins as a red papule at the site of the initial tick bite. The papule gradually enlarges, usually over days to weeks, with an advancing red border and central clearing as shown on the thigh of a patient. Multiple lesions can result from multiple tick bites or from hematogenous dissemination of spirochetes to distant cutaneous sites.—*Mark Lebwohl, MD, and Stephen Kurtin, MD*



Radiology Notes

Pulmonary and Skeletal Tuberculosis

A 58-YEAR-OLD African-American man, who had been treated for pulmonary tuberculosis 12 years previously, presented with weight loss, cough, and a painful, swollen left wrist of several months duration. A chest x-ray demonstrated bilateral upper lobe fibrotic changes to both apices with nodules, and bilateral pleural thickening. These findings were more prominent when compared with earlier chest x-rays. The sputum smears were negative for acid-fast bacilli. An x-ray of the left wrist demonstrated erosive cystic changes of the scaphoid bone, as well as soft tissue swelling. The patient was treated empirically with isoniazid, ethambutol, pyrazinamide, rifampin, and vitamin B_6 for pulmonary tuberculosis and tuberculous osteomyelitis. When the patient underwent a tenosynovectomy of the wrist, a caseating granuloma was found. However, no acid-fast bacilli were seen, and cultures of the synovium did not grow out acid-fast bacilli.

One month after initiating treatment, *Mycobacterium tuberculosis* was identified in cultures of sputum taken before the synovectomy. The patient is doing well 6 months into his treatment.—*Howard S. Blaustein, M.D., and Maryanne Wysell, M.D.*

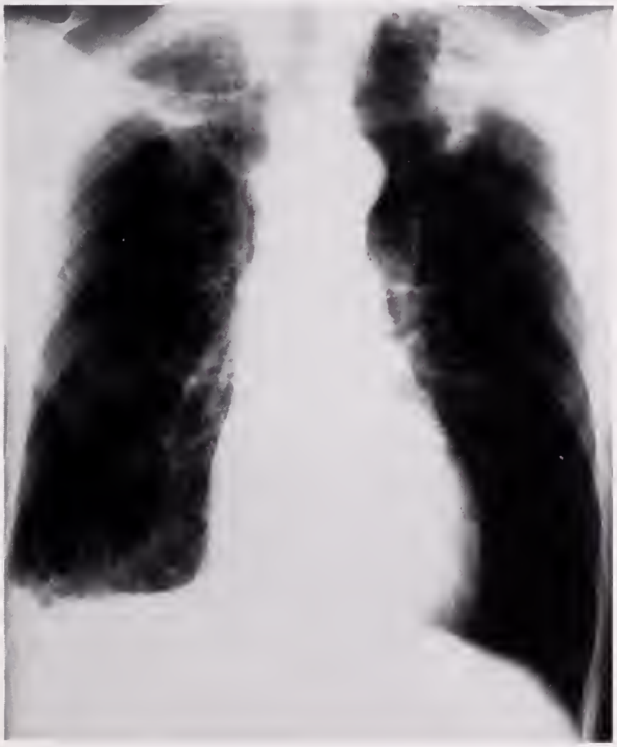


Fig. 1.

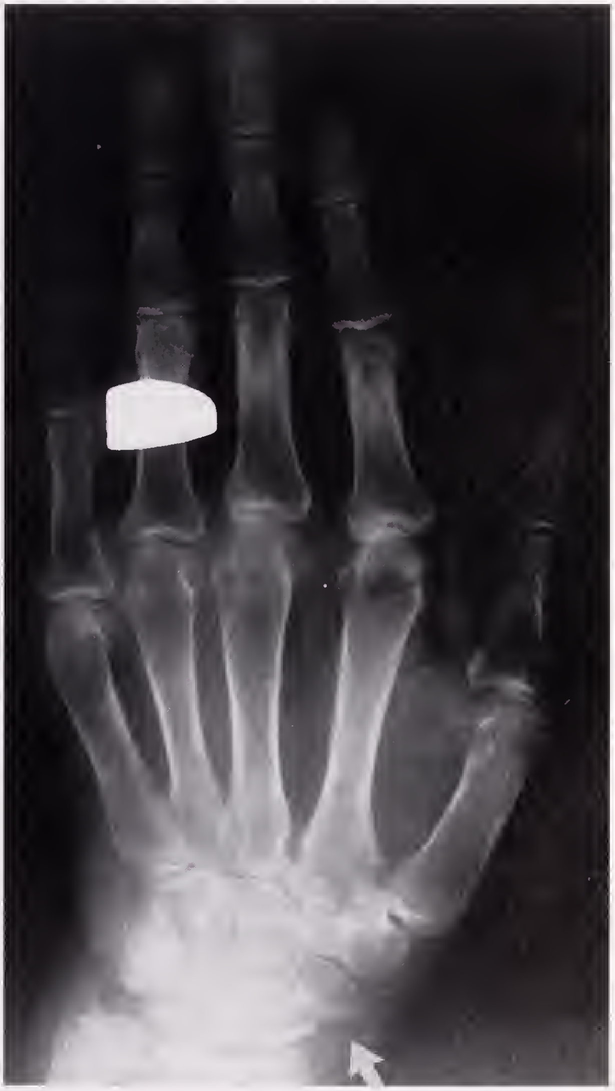


Fig. 2.

Book Reviews

American Cardiology: The History of a Specialty and Its College

W. Bruce Fye. Baltimore, London: Johns Hopkins University Press, 1996. 489 pp, $24.95. ISBN 0-8018-5292-7.

Consider this: The American College of Cardiology, created in 1949, had 275 attendees at its first national meeting in 1951. At that time, there were 442 Fellows. At the 1995 meeting, 25,000 attended and the College had 22,240 members. The American Heart Association, founded in 1924, had 200 at its first meeting and attendance similar to the College at its most recent meeting. The first electrocardiograph in the United States was located at The Mount Sinai Hospital in 1909. In 1940, there were only four residency positions in cardiology in the United States. By 1952, there were 27 approved training programs in Cardiology offering 36 first-year and 25 second-year positions. Presently, there are 210 Cardiology Fellowship programs with 2,633 trainees. Between 1965 and 1979, the membership of the American College of Cardiology tripled and the number of board-certified cardiologists in the United States increased sixfold.

This parallel and rather startling growth of the American College of Cardiology and the specialty of cardiology are analyzed nicely, with precision and writing flair by W. Bruce Fye, M.D. Fye's titles, Chairman, Cardiology Department, Marshfield Clinic, Wisconsin, and Adjunct Professor of the History of Medicine and Clinical Professor of Medicine, University of Wisconsin, indicate the fortunate mixture of clinician and historian which enable him to analyze the scientific, sociological, political, and yes, psychological factors fueling this growth. He does this by meticulously reviewing pertinent oral history and the appropriate documents. We cannot appreciate all of the nuances involved in other historical developments without analysis of the psyches and motivations of the principals. Similarly, advances and changes in cardiological organizations and in the practice of the specialty are understood better by Fye's articulate analysis of the personalities, social and ethnic backgrounds of leaders and "wannabees" of American Cardiology in the 1950s and 1960s. It is interesting that the "outs" of that period, who formed the American College of Cardiology, were more aggressive, more foreign, and from different ethnic backgrounds than the "ins" controlling the American Heart Association. They therefore appreciated the growing needs of clinical cardiologists more precisely and in a more timely manner than did the established leaders of the reigning American Heart Association.

Fye explores well the reasons for this and the concomitant sociological, political, and scientific developments in the United States shaping modern cardiology. He traces the growth of the American College of Cardiology, its important journal (in which the cardiologists from the Mount Sinai Hospital had key roles), the development of its main teaching facility, Heart House, its educational outreach to a variety of international venues, its innovative teaching techniques, such as audience-participating Fireside Conferences and "how to" sessions, all of which had a major worldwide impact on postgraduate education in cardiology. He relates the rapprochement of the American Heart Association with the American College of Cardiology which mollified ruffled egos. The now parallel organizations have further catalyzed the advance of cardiological research and education. This treatise enables the reader to appreciate a vibrant specialty which has made many remarkable advances in a relatively short time. Fye's analysis of these advances and what he perceives to be trends for the future in cardiology make an intriguing and pertinent book that should be of interest to physicians, sociologists, and historians. This important tale, written in a scholarly, fascinating, and interesting manner, is a fine contribution.

Leslie A. Kuhn, M.D.
Mount Sinai School of Medicine

Grief and AIDS

Lorraine Sher, editor. Chichester:
John Wiley & Sons, Inc., 1995.
215 pp, $14.95.
ISBN 0-471-95346-6.

and

Good Doctors, Good Patients, Partners in HIV Treatment

Judith Rabkins, Robert Remien,
Christopher Wilson. New York:
NCM Publishers, Inc., 1994.
201 pp, $ 15.00.
ISBN 0-964-38840-5.

It is with painful and inextinguishable clarity that I remember the first time I knowingly spoke dishonestly with a patient. It happened in 1981, on an autumn day every bit as clear, crisp, and vibrant as the day on which I am composing this review. Each of us was new to our calling. He was a young gay architect dying in Bellevue Hospital. My career as a physician commenced in Year 0 of the epidemic, and he was a patient during my first clinical clerkship. He was one of the first to sicken and die in the epidemic.

He had one of the first cases of Kaposi's sarcoma reported in gay men. His skin was dotted with Kaposi's lesions. He was severely cachectic. His diarrhea was unremitting. His voice was weak and tremulous. His movements were slow. Ordinarily, he said little as if to reserve his meager store of energy and to keep it from draining out in sustained verbal exchange. When he did speak, it was usually to make a specific request for help or to express gratitude for the care which had just been tendered.

Sometimes I would pull up a chair and sit with him in silence. On one of these occasions, he broke the silence with a simple question. He asked me if he was dying. I remember looking up to the window which faced north high over the East River. Spreading out to the horizon lay water, city, sun, and sky, all sparkling with light and pulsating with movement. I avoided his cadaveric gaze and spoke to this expanse when I responded that I did not know if he was dying and that I hoped that he would get well. Deep in my heart or bones, or wherever such knowledge resides, I knew, of course, he was dying. And so did he. Turning away from the truth left him stranded alone until he might venture again to find someone with whom he might speak about dying.

My failure of empathy and candor can be examined from several perspectives. On the level of individual analysis, my inexperience offers a ready explanation. However, taking a broader view of the state of American medicine and culture at the advent of the AIDS epidemic is more instructive.

From a scientific viewpoint, all we had was perplexity and helplessness in 1981. The patient's disease was not yet named; its nature and outcome were unknown. Candor is hard to come by when knowledge is sparse and uncertainty reigns. So even if he had addressed his question to a more experienced clinician, he might not have received a more honest response.

Looking at my evasiveness from a cultural point of view, it is easy to see that it manifested a dominant norm of repression and inhibition: death was still in the closet. Kubler Ross' seminal explorations were just coming to public and medical awareness. We were still launching wars on cancer and other threats to the illusion of American omnipotence and invulnerability. At the advent of the AIDS epidemic, death meant defeat and failure in the medical world. Dying did not signify the final phase of life through which patients must pass with the help of their physicians, which is how it is conceived by the two books under review here.

When the epidemic began, physicians did not speak usefully or well to patients about dying. Since then, much has changed in the approach of American medicine and culture to issues of death and dying, and much of this change has been fostered and shaped by the epidemic. *Grief and AIDS* illustrates how AIDS has put death on our clinical, psychological, and cultural map. This is an eclectic collection of essays by AIDS researchers and health care providers in Canada, England, Australia, the Netherlands, Uganda, and the United States. The editor, Lorraine Sher, is a psychologist and AIDS researcher, at the University of London. The essays encompass the topics of illness, dying, death, survival, mourning, grief, and psychiatric disorder in a wide ranging fashion. Overall, the quality of the essays varies greatly. Although there are a few good essays which touch on disparate aspects of the epidemic, overall there is a choppy, unintegrated feel to the collection.

In a well-written essay, Laura Dean reports on a large, longitudinal study of psychological distress in gay men, which has been conducted since 1985 by a team of psychiatric epidemiologists at Columbia University. There is an instructive and gripping essay by Frans M. van den Boom from the Netherlands reviewing recent studies of psychological morbidity and developmental problems in children whose parents died of AIDS. There is an essay on the psychological and economic strains of repeated AIDS deaths on Ugandan families observing traditional norms of burial and mourning. This slender, moving essay by two health care workers in Entebbe compels one to reflect on the global character of the epidemic and on the profound differences in its manifestations in other cultures. There is also a dry but useful survey of the literature on "burnout" in health care providers.

Sandwiched between these epidemiological and anthropological bookends are essays concerning the clinical, ethical, and legal issues which arise in the care of the dying patient ("Allowing Someone to Die"; "Living Wills"). These are tangential to the principal focus on grief, are less well written, and not particularly enlightening.

Finally, there is a core bundle of essays which focus on the phenomenology of bereavement, grief, coping, adaptation, and the psychological morbidity associated with loss. These focus on the grief of surviving partners, children, parents, siblings, and health care workers. They are uneven in quality; some have only the minimal coherence of a catalog of topics.

Most of all, what is missing here is an effort to glean from the AIDS experience and AIDS research some better understanding of the human psyche, and how it is affected by one's own approaching death or the death of others. One would expect that extensive social and clinical scientific study during an epidemic would yield a deeper appreciation of what grief is and why we have the reactions we do when we lose those to whom we are attached. The death of a loved partner, a parent, a child, or a patient is not just another "psychosocial stressor." It moves us in some fundamental way. If we do not actively resist the impact of such a death on our psyche through psychological defense, the experience seizes our whole being. That something deeper is afoot with grief than other distresses in life is reflected in the fact that other kinds of mammals mourn the death of group members, and even the deaths of members of other species.

Separately and together, these essays do not deepen our understanding of these phenomena. Because of the diversity and unevenness of this collection, this volume has limited utility. Summaries of the research literature might be useful to psychologists and psychiatric epidemiologists working on AIDS-related problems. For medical and mental health clinicians working with AIDS patients, their family members and friends, its value is nugatory. For clinicians in the American urban areas, these limitations are especially severe. No attention is paid to the variations in the forms and practices of dying and grieving among the ethnic groups afflicted by the human immunodeficiency virus. For a multiethnic society, such a lapse is a serious deficit.

With the second volume under review, *Better Doctors, Better Patients: Partners in HIV Treatment,* the situation is altogether and happily different. This superb volume was jointly authored by Judith Rabkin, Robert Remien, and Christopher Wilson. Drs. Rabkin and Remien are psychologists; Mr. Wilson is a nurse. All three have been studied and published extensively on the psychological dimensions of HIV disease over the past decade. Equally important, they have been involved in the care of many individuals with the HIV infection.

The principal focus of this well written, moving volume is the relationship between physicians and their patients who are afflicted or will be afflicted with the sequelae of HIV infection. As the title indicates, this is an exploration of how partnership can make for better doctors and a better experience for patients. This, of course, is no simple matter with a disease with a long, slow, uncertain course ending in death.

The exploration of the relationship works along two dimensions. At a social, historical level, it depicts the onset of the epidemic, the dearth of information, and the attendant panic and despair of the early years, and it examines how these served to pull the traditional paternalistic doctor-patient relationship in the direction of a model of shared decision-making. Several factors contributed to this transformation. The paternalistic model was already under duress as relationships of control in many domains of life came under critical scrutiny. The affliction of gay men in New York and San Francisco meant that a politically activated group, which had previously been shortchanged by the medical establishment and which was already in political and cultural revolt, would have something to say about the character of medical care it would need. And most important, the fundamental, bedrock difference between doctors and patients, the disparity of knowledge of the disease and the tools to cure or control it, were gone. In the first years of the epidemic, doctors and patients were huddled together on a level playing field.

The second level of analysis is individual and psychological. The authors argue that with the growth of scientific knowledge and clinical experience, HIV infection must be approached as a chronic, progressive disease. Physicians and patients, if they are engaged in a real therapeutic partnership, can work to establish a balance of hope and realism appropriate for each stage of the disease. The authors guide the reader through the stages of the disease, from the psychologically catastrophic moment of serodiagnosis, through the asymptomatic years in which health maintenance is the focus of clinical work, on to the years of opportunistic disease and illness, and, finally, to the terminal stage of the infection. At each stage of the disease, there is a discussion of the tensions, uncertainties, and differences that can arise, such as the use of antiretroviral medications in the asymptomatic phase of the illness, or the cessation of aggressive measures to hold off disease progression in later stages of the illness.

Although the authors' commitment to a model of partnership and shared decision-making is complete, there is an interesting and subtle discussion about how patients may need to seize or relinquish control of care in different circumstances and about how the physician can adjust to these perturbations in the partnership while working toward its restitution.

The distinctive excellence of this book is the merger of scientific knowledge and clinical medicine with a sophisticated appreciation of the "interpersonal field" of patient and doctor. The authors accurately capture the desires, needs, and fears of both doctors and patients, as they work to stave off disease progression and decline. Their account of what goes on between doctor and patient is complex and nuanced. They weave a decade of research about the psychological distresses of HIV infection into a readable narrative about the experience of doctors and patients. Although much of what the authors report about the varieties of patients' experiences can also be gleaned from clinical and lay literature on AIDS and from contemporary AIDS fiction, they make a special contribution by interpolating extended passages of physicians' reporting on their own experiences with patients. These are particularly riveting and instructive in the final phase of the disease in which the physicians and patients deal with deterioration and death.

The chapters in the last part of the book are entitled: "Balancing Hope and Candor," "When Physicians Can't Cure Patients," "The End of the Line . . . When Enough is Enough." Although they deal with the clinical issues which arise in the terminal phase of AIDS (wasting, blindness, dementia, isolation), the psychological issues for physicians transcend these specific circumstances. This volume will be rewarding to anyone helping with AIDS patients, including patients, their loved ones, and their caregivers. But in these final chapters, the volume transcends itself as an essay on AIDS care. *Good Doctors, Good Patients* can enlarge our understanding of the best that can transpire between physician and patient when one shepherds the other through the final stage of dying of any disease. Years ago, it would have better prepared me and my teachers to help my patient with his death.

Michael Teitelman, Ph.D., M.D.
Mount Sinai School of Medicine

Patient or Pretender: Inside the Strange World of Factitious Disorders

Mark D. Feldman and Charles V. Ford with Toni Reinhold. New York: John Wiley & Sons, Inc., 1994. 228 pp, $14.95. ISBN 0-471-12013-8.

Sick people want to get well, the sooner the better. Physicians are educated and naturally attuned to help achieve such an outcome. Patients with a factitious disorder, better known as Munchausen syndrome, confound us because they do not want to get well. To remain ill, they create and feign illness. Most patients with a factitious illness spend much of their lives in doctors' offices, confounding their caregivers with fanciful inventions of illness and lies, undergoing multiple invasive and noninvasive investigations, and entering hospitals intermittently. The more seriously affected spend much of their lives as hospital inpatients and undergo multiple surgeries. Patients with factitious illnesses are aware of what they are doing but do not know why they are doing it.

This bizarre deviation from the expected continues to fascinate, confound, and upset physicians. So imperative are physicians' needs to diagnose and treat illness, and so compulsive is the need of patients with factitious illnesses to create illness and to disguise its true origin, that the condition is frequently misunderstood and probably underdiagnosed. Only when the patient actively drops glaring clues about his activities, virtually rubbing the medical staffs' faces in the way he is creating illness, do physicians begin to entertain the possibility of factitious illness. Then, confronted with evidence of the deception and feeling their faith in their diagnostic acumen and desire to heal undermined, physicians may erupt in rage. The patient then attempts once again to reestablish his bona fides as a genuinely ailing human being by creating maladies anew and eliciting sympathy from staff members not inclined to accept the possibility of the factitious nature of the illness. The result, well known to hospital administrators and patient representatives, is never less than explosive.

The plethora of articles describing some aspect of the clinical presentation of patients with Munchausen syndrome, usually grouped according to organ system, does not seem to have significantly increased awareness about the illness. Commonly overheard in the halls of hospitals, even among the most experienced and sophisticated, is the statement, "But, they have real illnesses!" This statement serves to illustrate the continuing confusion in distinguishing factitious illness from hypochondria, in which patients *imagine* they are ill but do not *create* illness. Malingerers, patients who feign illness for a particular purpose, add to the diagnostic confusion. For example, a homeless person, seeking a meal and a place to stay overnight, may complain of a set of symptoms to arrange for hospital admission. He does not *create* medical disease and his symptoms quickly disappear once his goal is achieved.

If factitious illness is so difficult for the physician to understand, can we expect the layman to fathom its subtleties? Publishers maintain that there is no subject which cannot be clearly explained in print. Perhaps. In their book about factitious disorders, Mark D. Feldman and Charles Ford, with the collaboration of journalist, Toni Reinhold, have certainly made a valiant attempt. In some respects, they have succeeded. The cover of the book has a banner headline, "As featured on Donahue, 20/20, and Good Morning America," revealing that the book is primarily intended for a lay audience. To simplify such a complicated subject, they have dwelt on the fascinating and bizarre aspects of the illness. They have gleaned their clinical material from the literature and from their personal experiences. They provide anecdotal descriptions of encounters with patients who have factitious illnesses. They switch to the term *factitial* illness, perhaps attempting to follow the terminology of the "Diagnostic and Statistical Manual," classifying *factitious* illness and Munchausen syndrome as synonymous. *Factitial* illness gives them the leeway to include all manner of clinical presentations in which patients have feigned illness but do not necessarily fall into the Munchausen syndrome category.

The authors maintain that many of these patients have responded to treatment. "Jenny," the first case they describe, is a young woman who begins to feign serious physical illness after a breakup with her boy-friend. She is treated for depression and appears to get better. She then starts to mutilate herself. With the aid of psychotherapy on a psychiatric service, both individual and group, she makes considerable progress and is discharged. In the following 2 years, her father, who has been instructed to call if the patient resumes feigned illness, has not contacted the author involved. Here, the authors may have missed some essential ingredients of the clinical course of patients with factitious disorders. The patients may, in fact, appear to improve, only to leave psychiatric treatment and suffer further illnesses at a later date, and in a different locale. Jenny's history of resumption of symptoms, despite seeming improvement after antidepressant medication and impending discharge, suggests that Jenny will be heard from again—most likely, after another romantic failure or loss. In addition, parental involvement in the enabling of factitious illness pathology is common, so we have no way of establishing her father's reliability. Moreover, patients with factitious illnesses are not amenable or susceptible to psychiatric treatment, irrespective of the depth of their pathology. However, they use and abuse the psychiatric situation to prove to their caregivers that they are genuinely interested in improving their lot.

The authors are correct in maintaining that some patients are more severely disturbed than others and they classify them as patients with true Munchausen syndrome who are end-stage, peripatetic, chronically hospitalized people. Indeed, most patients with factitious illnesses do not belong to this category and have intermittent episodes. They may appear to be cured between episodes. But, the authors' depiction of factitious illness as an "exaggerated outgrowth of a relatively harmless, normal childhood behavior of 'playing sick' " is not tenable. Surely, the normal child, who tells his mother he is ill to be close to her or to avoid some harrowing condition at school, bears no resemblance to a chronic psychopath who devotes his life to injuring himself in some of the most bestial ways in order to remain ill.

The authors emphasize the etiological importance of the quest for care and attention, while failing to stress the more important impact of early abnormal personality development, childhood events relating to illness in the patient and family members, loss, and somatization in family members. Suggesting "the need for attention" as an etiological agent generally bespeaks a lack of sophistication in the understanding of the mind's operation. The authors do allude to the need in these patients to gain control by feigning illness and to avoid painful emotions by focusing on their bodies. One can see the conflict the authors must have had in deciding to write a book for a lay audience. Is it possible to be academic and appeal to an unsophisticated readership at the same time?

The authors devote several chapters to illustrating the many ways in which patients with factitious illnesses create their illnesses. They do so in the time-honored way of describing the clinical pictures based on individual organ systems. This is deceptive. For example, although a patient may present at any given time with a self-induced hematuria, this does not mean that his fabrications have been limited to or will be limited to this organ system. In fact, the opposite is true. Any one presentation represents only the tip of the iceberg of the total clinical picture over time and in different geographical settings with different physicians and hospitals.

The book contains an excellent chapter on Munchausen by proxy, a frightening off-shoot of factitious disorder in which mothers, and on rare occasions, fathers, fabricate illness in their children. The subject is topical and is given full weight by the authors. In addition, they fully discuss the ethical implications posed when doctors want to expose these patients to prevent future admissions, endless invasive and noninvasive procedures, all at considerable cost. They are not as optimistic about outcomes in their final chapter, suggesting again how difficult it is to present a totally pessimistic attitude in a book for the lay reader.

Overall, the book is easy to read and the hand of a professional journalist can be seen throughout. The device of letting each of the authors speak from personal experience works well. The lives of patients with factitious illnesses are never dull.

Berney Goodman, M.D.
Mount Sinai School of Medicine

What Works: Reducing Re-offending, Guidelines from Research and Practice

James McGuire, editor. New York: John Wiley & Sons, Ltd., 1995.
viii + 242 pp, $32.95.
ISBN 0-471-95053-X.

In 1974, an article by criminologist Robert Martinson in *Public Interest* (10:22–54) concluded that there was no reliable evidence that criminal offenders could be rehabilitated. The subsequent years witnessed policies of hard sentencing, new prestige for biological/genetic theories of the origins of crime, and abandonment of the treatment ideal.

In several countries, since the end of the 1980s, several researchers challenged Martinson's "nothing works" philosophy and developed new projects, data, and measurement techniques. Some results of this new look at the possibility of effective rehabilitation appear in this book, with contributions of authors from England, the United States, Canada, and Germany.

The chapters deal with an overview, meta-analysis, cognitive training, matching service and clients, community-based programs, diversion from prosecution, program management improvement, treatment of sex offenders, and evaluation.

A summary of three of the chapters, which are representative of the total, follows.

A meta-analysis of 400 studies on the effectiveness of treatment with juvenile delinquents, conducted by psychologist Mark W. Lipsey of Vanderbilt University, found a 10% decrease in the recidivism rate of the treated subjects when compared with untreated or control groups. This is a statistically significant difference even though it may appear to be relatively small. Analyzing specific programs, those that targeted behavior for change and approached it in a relatively structured fashion were more likely to be successful than targeting psychological processes for change. The widely publicized "boot camp" or shock incarceration programs actually resulted in increases in delinquency.

The importance of type of treatment is illustrated in Lipsey's finding that some of the most effective treatments were as effective in the lower dosages as in the higher dosages. Thus, the type of treatment was more powerful than its sheer amount. Several other similarly very clear findings emerged when meta-analytic statistical techniques were used.

A chapter on treating sex offenders by Robert Prentky summarizes a study conducted at the Massachusetts Treatment Center. Using postdischarge freedom from re-arrest for 5 years as a measure of recidivism, 25% of the treated offenders were re-arrested versus 40% of the control group. The chapter sets forth a rationale for different approaches to treatment that is quite encouraging in view of the usually gloomy outlook for such cases.

A third chapter, by Don Andrews of Carleton University in Ottawa, presents a clinical criminological approach that is empirically defensible and whose applications are promising for the design and delivery of effective direct-service programs. This model is based on a psychology of criminal conduct (PCC) that is open to the full range of correlates of criminal conduct. PCC has demonstrated its ability to predict, explain, and influence criminal activity. This PCC respects diversity and provides detailed suggestions for modes and styles of treatment service targeted to those at risk for criminal conduct and in need of effective rehabilitation. The discussion concludes that a clinical approach informed by a psychology of criminal conduct can provide the basis for positive developments in rehabilitation.

Charles Winick, Ph.D.
City University of New York
Graduate School

Comparative Vertebrate Neuroanatomy, Evolution And Adaptation

Ann R. Butler and William Hodos.
New York: Wiley-Liss, 1996.
552 pp, $74.95.
ISBN 0-471-88889-3.

INITIALLY ONE might look at the title of this book and say, "Why would I need this?" However, the book is both interesting and informative, not only to a specialist in the field, but to the scientifically literate reader as well. Moreover, the book is refreshing in its daring approach. For example, the authors depart from the traditional concept of 12 cranial nerves to include discussions of other cranial nerves found in vertebrates (e.g., terminal, epiphysial, and lateral line nerves). The anatomy of these nerves, which is integrated into the discussion of their evolution and various functions, provides a functional view of the vertebrate nervous system which makes good sense. Another admirable aspect of the book is that the authors provide an evolutionary perspective for many of the topics. Their aim is to show that brain complexity grew out of a need to adapt to the environment, not as a result of evolving up the evolutionary scale (e.g., from fish to rats to humans). The book is very well written and easy to read. One can enjoy reading the sections on evolution and the interesting tidbits on comparisons across species without getting bogged down in neuroanatomical particulars. For example, the chapter on the reticular formation (a brain area often viewed as complicated or boring) contains fascinating discussions on the organization, function, and evolution of this structure. For the student, this serves to underscore the importance of grasping the neuroanatomy.

The chapters are organized by brain region in a manner similar to a typical neuroanatomical text. One nice feature is that each chapter has an introduction which summarizes the material that will be covered and puts the topic into an overall perspective. Other assets are the appendix and the glossary of terms at the end of the book. These are helpful to students and to anyone whose expertise does not encompass all of the fields covered in this text.

The one major weakness of this book is its illustrations. Although economic considerations may well be the culprit here, the visuals were disappointing. For example, there are few photographs of brains. Most of the figures are drawings which merely outline the various brain regions in different vertebrates. Ideally, figures should emphasize a point, provide a means of visual comparison, or in some way save the reader a thousand words. The illustrations fall far short of this goal.

It is difficult to decide who would use this book. The authors state that the book is meant for students of neuroscience at the graduate or advanced undergraduate level. Certainly, it could be recommended as a course text for advanced students of zoology or evolution. This text would provide important and relevant background for courses such as evolutionary biology, comparative neuroanatomy, and possibly even veterinary medicine. However, a previous course in human neuroanatomy would be necessary, because the student must have a clear idea of what the different brain areas look like in primates (this book relies heavily on fish brains). This text would not be particularly suitable for courses in neuroscience or medicine because it covers material specifically related to comparative nervous systems. Despite its somewhat limited utility as a course text, this book would make an interesting addition to the libraries of students of neuroscience or of science in general. Teachers of neuroscience may wish to add this book to their libraries as an excellent resource book.

The highlights of this book are its scholarly integration of material on the nervous system and evolution, and its excellent treatment of the cranial nerves. A goal of the authors was to write a text at a level suitable for both students and science enthusiasts. This is always a demanding task. For instance, the amount of neuroanatomical detail is too much for the enthusiast, but fine for the advanced student. Fortunately, the text is written in such a way that the reader can glean as much or as little neuroanatomical detail as desired. In this respect, the authors have succeeded in their purpose.

Marilyn Y. McGinnis, Ph.D.
Mount Sinai School of Medicine

The Handbook of Self-Concept: Developmental, Social and Clinical Considerations

Bruce A. Bracken, editor.
New York: John Wiley & Sons,
1996. 539 pp, $59.95.
ISBN 0-471-59939-5.

References to our *selves* and to the self of others are ubiquitous aspects of everyday life: self-concept, self-acceptance, self-esteem, self-image, self-efficacy, you, your, yourself, etc., etc. We spend large amounts of time focused on issues related to the self—yet how much time has any of us spent attempting to understand the scholarship on the topic? For those who would answer not enough, this volume edited by Dr. Bruce Bracken will greatly facilitate remedial efforts.

Harter's opening chapter is a comprehensive tracing of the key issues in self-concept theory and research, from William James' distinction in the 1890s between the subjective self (organizer and interpreter of experience) and the objective self (all that is known about the self), to such current work as Bandura's emphasis on the functional role of self-representation. Next Marsh and Hattie review structural models of self-concept, ranging from a unidimensional, general-factor model to a variety of multidimensional models. They also devote a section to the ways that the relationship between global self-concept and the subcomponents of it have been conceptualized. In Chapter Three Keith and Bracken provide a brief background regarding the approaches that have been used to measure self-concept. They evaluate 20 of the more important measures that have been developed, ranging from the early attempts (Rosenberg Self-Esteem Scale) to current work (Multidimensional Self-Concept Scale).

The next section of the book narrows in focus to examine more specific aspects of the multidimensional structure of self-concept. Berndt and Burgy begin with a chapter that covers the measurement of social self-concept and its interrelationships with other variables. The Novick, Cauce, and Grove chapter does not follow the breakdown of general self-concept into self-conceptions regarding specific domains (e.g., academic, social, physical) but rather focuses on competence self-concept. These authors note that most self theorists view self-efficacy as central to this construct. In addition to a brief discussion of theory, they review developmental issues including substantial discussion of work on adults, as well as a welcome section on the impact of sociocultural resources.

Prout and Prout suggest that during treatment planning, clinicians consider whether the presence of self-concept problems is the cause or effect of a particular disorder. They go on to review the relationship between global self-concept and situational factors, disabilities, health and psychological problems. Byrne discusses support for the notion that although self-concept is clearly multidimensional, one of those dimensions, academic self-concept, is also multidimensional. She also reviews evidence regarding the causal direction issue discussed in the previous chapter and notes that whereas many earlier studies were equivocal, more recent (and more rigorous) research seems to be favoring the view that academic self-concept predicts subsequent academic achievement We should note that Byrne has a new volume on measuring self-concept across the life-span that should be available by the time that you read this (1).

Feiring and Taska cover the concept of the self in the context of the family. Stein's chapter focuses on physical self-concept, an important area, even if we restrict our attention to children. She notes that, "because children as early as first and second grade are cognizant of their body shapes and sizes and actively attempt to modify them," additional research in this area may aid in the development of effective strategies for the prevention of eating disorders and obesity (p. 388). Crain reviews the research on the relationship between self-concept and age, race/ethnicity, and gender. She concludes that differences that have been observed are not large enough to be considered clinically meaningful.

Hattie and Marsh's chapter explores their views on the future of self-concept research. Some errors in this chapter limit the utility of the information; however, the conclusions are a useful summary of research that needs to be done in the future.

In the final chapter, Bracken presents an overview of his Multidimensional Self-Concept Scale (MSCS), which is based on a behavioral conception of self-concept. He also provides a case study that provides the reader with a view of the potential clinical utility of using the MSCS. In closing, we thought that Prout and Prout provided a succinct rationale for the importance of clinicians learning more about self-concept.

> Self-concept is a complex psychological construct that has a long history and pervades a wide variety of psychological theory and practice. In clinical practice, self-concept issues

> are often the base of psychological and educational referrals, a focus of clinical assessment, and a target for treatment. . . . Many wide-ranging psychotherapeutic approaches (from psychodynamic to cognitive-behavioral) point to self-concept and its associated variables as significant in their theoretical formulations (p. 259).

Self-concept is central to clinical work, and this comprehensive treatment of the topic will be central to discussions of self-concept for a long time.

Reference

1. Byrne BM. Measuring self-concept across the lifespan: Methodology and instrumentation for research and practice. Washington, DC: American Psychological Association; 1996.

Gary Rosenberg, Ph.D.
Mount Sinai School of Medicine
Gary Holden, D.S.W.
Ehrenkranz School of Social Work
New York University

Disorders of Personality: DSM-IV and Beyond

Theodore Millon with
Roger D. Davis and contributing
associates. New York:
John Wiley & Sons, Inc.,
1996. 2nd ed., 754 pp, $79.95.
ISBN 0-471-01186-X.

THE FIELD of personality disorders is a complex and ever-changing one; diagnoses shift, treatments change, and the patients are among our most challenging. This monograph provides a comprehensive overview of the field. Theodore Millon is Professor of Psychiatry at Harvard University and is recognized as one of the leading authorities of the field, and as such, he is uniquely placed to write this volume.

The preface indicates the inordinate growth in the field over the past 15 years, during which it has finally "come of age." The text thereafter is divided into two parts: the first addresses the conceptual underpinnings of personality disorder and the second devotes a chapter to each disorder. Initially personality is defined and the limits of the Diagnostic and Statistical Manual (DSM) as a descriptive tool are delineated. Classification is discussed with emphasis on dimensional models and prototypes; from there the intriguing history of the field is charted, beginning with the early Greeks, moving through the early theorists of this century including Kraepelin and Kretschmer, Freud and Fromm, to the contemporary thinkers including Kernberg and Kohut, Stone and Sullivan. Last, Millon's own models are described. A review of the development of the DSM is especially helpful. Personality development is the focus of the third chapter; biological factors and experiential history are discussed, and neuropsychological development and stages are detailed. A description of functional and structural domains relevant to personality disorder follows; the former referring to dynamic processes and the latter to the person's enduring template of memories, attitudes, and fears. A concise summary of assessment instruments precedes an elegant journey through the land of personality therapy, beginning with eclecticism, our current treatment philosophy, and tracing the development of integrationism, from which Millon's new model, personologic psychotherapy, is derived.

The remainder of the text groups the personality disorders into four clusters. Thus Schizoid, Avoidant and Depressive Personality Disorders are denoted "Pleasure-Deficient" and Dependent, Histrionic, Narcissistic, and Antisocial are "Interpersonally Imbalanced." "Intrapsychically Conflicted" comprises the Sadistic, Compulsive, Negativistic, and Masochistic; and Schizotypal, Borderline, Paranoid, and Decompensated are "Structurally Defective." Disorders other than those in the DSM-IV are included and a valid argument for each proposed; the DSM classification into eccentric, dramatic, and anxious clusters having been dismissed as having little validity earlier in the text. Each personality disorder is gracefully described. History, clinical features, and pathogenic developmental background are elucidated, with therapeutic strategies concluding each chapter. The clinical descriptions are particularly well done and include prototypal variants, comorbid disorders, and case studies. Treatment deals with each modality in turn and alludes to resistances and risks inherent in the therapy. The final chapter describes decompensated personalities, the concept of severity being all but ignored in DSM.

There are no omissions; the only fault may be that of repetition, but even this serves to make the text more compelling. *Disorders of Personality* more than fulfills its mission. It provides psychiatrists, psychologists, and others with a strikingly comprehensive review of this complex area, and reminds us that a beautifully written volume can stir the interest even of those who would not ordinarily be so inclined.

Richelle Kirrane, M.D.
Mount Sinai School of Medicine

Hives of Sickness, Public Health and Epidemics in New York City

David Rosner, editor. New York:
Museum of the City of New York,
1995. 223 pp, $35.00.
ISBN 0-8135-2158-0.

THIS VOLUME is a collection of essays written by nine historians of American medicine, chronicling and examining aspects of New York City's response to its public health problems from colonial times to the present. The obvious objective of this volume is to present the demographic, social, economic, and political conditions that affected the development of public health policy and practices rather than to detail the scientific discoveries and rationale that lead to changes in public health epidemiology and practices.

As can be expected in any collection of essays, some are more successful than others. However, the overall volume makes an important contribution to the history of public health practices in New York City and affords a greater understanding of the development of public health policy toward current problems, including AIDS and the reemergence of tuberculosis.

The volume begins with a presentation by Gretchen A. Condran of the changing patterns of epidemic diseases in New York City. This essay provides an epidemiologic overview of the prevalence of various diseases, especially infectious diseases, that were the focus of health policy changes and development since the late 1700s. The tables serve as a quick reference for quantitative data.

Elizabeth Blackmar reviews the approaches of the city government to the regulation of housing and the maintenance of public sanitation in the city. In a fascinating overview entitled, "Plagues and Prejudice," Alan M. Kraut explores the effects of immigration and the prejudices of the resident population in New York City in determining public health policy. The city is still a center of immigration in the United States and this historical presentation has much applicability to the present. The essays on various infectious diseases, including small pox, polio, and AIDS, present the effects of epidemic diseases on public policy, public bias and politics.

The last two chapters of the volume are concerned with the responses of the medical community to the epidemic diseases in New York City. This is a fascinating account of the establishment of the New York City Health Department in the late 1800s and the role played by leading academic physicians in New York City, especially Dr. Herman Biggs, who was the head of the Department of Bacteriology and Disinfection in the New York Health Department for many years. These chapters are especially interesting for the history of the interplay of organized medicine in New York City with the political machines, including Tammany Hall. The similarities between the development of the city health department's approach to diphtheria in the late 1800s and the early 1900s and the current AIDS epidemic seem to corroborate that history repeats itself. These chapters are especially successful in their recounting of how public health physicians in New York City, such as Herman Biggs, were quick to apply the results of the emerging field of bacteriology, lead by Pasteur and Koch in Europe, to problems of public health in an urban setting. Indeed, The New York City Department of Health became the model for health departments in cities in western Europe.

The volume may have been more useful if more quantitative epidemiologic data had been presented in tabular form in all of the essays. Nonetheless, this volume is a valuable contribution to the understanding of the history of the development of public health policy in New York City and, furthermore, will be useful for those attempting to understand the interplay of various factors in the development of public health policy, especially in urban settings.

Shalom Z. Hirschman, M.D.
Mount Sinai School of Medicine

Textbook of Psychiatric Epidemiology

Ming T. Tsuang, Mauricio Tohen, and Gwendolyn E. P. Zahner, editors. New York, Chichester, Toronto, and Singapore: Wiley-Liss, 1995. 483 pp, index, $59.95. ISBN 0-471-59375-3.

THIS TWENTY-CHAPTER textbook will be readily appreciated by anyone, novice and expert alike, interested in psychiatric research, teaching, and administration. The scope of information is almost encyclopedic. However, as must invariably be the case with a book written by many contributors, style of writing and authors' expectations of the reader's basic knowledge vary considerably from writer to writer. As such, this book might possibly best find its niche as the required text for a university course on psychiatric epidemiology.

Part I, entitled "Historical Overview," reviews the evolution of empirical research in psychiatry during the twentieth century. Divisions into first-, second-, and third-generation studies are somewhat artificial where such differences are essentially technical, e.g., changes in operating scales, statistical analysis, experimental design, clinical skills of raters, etc. Although this is not a textbook in philosophy or history, it would be helpful to trace how empiricism in psychiatry evolved both from, and parallel to, Husserlian phenomenology, existentialism, and psychoanalytic theory. A formal chapter on ethics would also be appropriate given some tragic excesses in twentieth century medical and psychiatric research.

The chapters on "Study Designs and Methods" (Part 2) and "Assessment" (Part 3) are very thorough and contain virtually every relevant variable and statistical consideration in use in contemporary psychiatric research and methodology. Some chapters, including "Methods in Psychiatric Genetics" and "Studying the Natural History of Psychopathology," are well balanced and read well. Others, such as "Analysis of Categorized Data: Use of the Odds Ratio as a Measure of Association," are tedious and hard to follow.

Part 4, Epidemiology of Major Psychiatric Disorders, is alone worth the price of the book. With the latest (and perhaps definitive) word on the statistics and current trends in research on schizophrenia, affective disorders, substance abuse, and personality disorders, the reader will be well equipped to follow current trends of psychiatric research into the twenty-first century. The only shortcoming in Part 4 is the too-short chapter on geriatric psychiatry, a reflection of the very limited attention given by DSM-III, -IIIR, and -IV to the elderly. Finally, the editors might reconsider a chapter on child psychiatry for a future edition.

S. L. Kushnir, M.D.
Mount Sinai School of Medicine

Pharmacology, Biology and Clinical Applications of Androgens: Current Status and Future Prospects. Proceedings of the Second International Androgen Workshop, Long Beach, California, February 17–20, 1995

Shalender Bhasin, Henry L. Gabelnick, Jeffrey M. Spieler, Ronald S. Swerdloff, Christina Wang, and Chuck Kelly, editors. New York, Chichester, Brisbane, Toronto, and Singapore: Wiley-Liss, 1996. 529 pp, index, $89.95. ISBN 0-471-13320-5.

It has become customary for workers in highly specialized fields to meet in informal workshops or miniconventions to discuss the advances in the field and to afford a forum for the exchange of their ideas and the results of their research. This volume contains the proceedings of the 2nd International Androgen Workshop held in February 1995. It appeared in mid 1996, thanks to the six editors, and thus makes the findings reported quite current.

Research on the androgens and testicular function have lagged behind the investigations of the ovary and its secreted hormones but, more recently, an attempt has been made to overcome this lag. These proceedings indicate the current boundaries in our understanding of androgen physiology and therapy. The topics covered are androgen physiology, androgen and the prostate, androgen effects on the brain (cognitive, sexual and aggressive behavior), effects on metabolism, androgen therapy, androgens and male contraception, and androgen delivery systems.

In the presentations and discussions, various investigators, generally leaders in their field, evaluate the present state of the art and attempt to bring the reader to the outskirts of current knowledge. As in any undertaking in which various investigators are given overlapping areas for discussion, there is a good deal of repetition. However, because “education is reiteration without irritation,” some repetition is not necessarily a fault. A major part of the focus is directed at the use of androgen therapy for male contraceptive purposes, but as yet no practical method has been established.

The use of anabolic steroids by athletes is generally an undercover operation; consequently, the lessons to be learned from the use of the anabolic steroids by the athletes are difficult to acquire. Indeed, it’s still not known whether use of anabolic steroids truly gives any real benefit to most of the athletes using such drugs. This workshop provides a good discussion of this problem.

An interesting section provided on the relation of androgens and the prostate has value for investigators in the field of prostate research. Topics also include the effect of androgen on bone, atherosclerosis, and hemopoiesis. All in all, the proceedings of this workshop would be of interest to workers in the field of androgen physiology and treatment, because it affords easy access to the boundaries of what is currently known.

The discussions are particularly interesting about what important fields are ripe for investigation and about which very little is known. The discussion on critical issues for the future by Nieschlag, Wilson, and Brown and Swerdloff affords insight into questions that need to be answered.

These proceedings will be of interest to all workers studying androgens, as well as to those who would like a quick insight into what is going on in research in androgen physiology.

J. Lester Gabrilove, M.D.
Mount Sinai School of Medicine

List of Journal Reviewers in 1997

Each year The Journal relies on its reviewers to actively participate in the selection of those manuscripts considered to be worthwhile, timely, interesting, and factual. The journal staff thanks the following reviewers for their time and intellectual effort.

Jack J. Adler
Arthur Aufses
Constance D. Baldwin
Peter Banks
Samuel Basch
Stephen G. Baum
Bernard Baumrin
David H. Bechover
Lawrence Berger
Howard Bernstein
Bruce Bochner
Edward J. Bottone
Howard W. Bruckner
Lewis Burrows
Christine K. Cassel
Carmel J. Cohen
Barry S. Coller
Felix A. Conte
Richard A. Cooper
Charlotte Cunningham-Rundles
Janet Cuttner
Michael J. Droller
Patrick Eggena
Joseph S. Eisenman
Luis R. Espinoza
Beth Essig
Solomon Estren
C. H. Evans
Michael J. Fellner
Raul Fleischmajer
Bruce Freundlich
Frederick Friedman
Harriet S. Gilbert
Paul Gilbert
Eli Ginzburg
Bernard Gondos
Bernie Goodman
Michael L. Greenberg
Adrian Greenstein
Vivek Gumaste
Richard S. Haber
Moshe Haimov
Jonathan Halperin
Noam Harpaz
Victor Herbert
Shalom Z. Hirschman
David S. Hodes
Steven Itzkowitz
Julius Jacobson
Sheldon Jacobson
Barry W. Jaffin
Robert Jones
Thomas Kahn
Mathew J. Kapklein
Andrew S. Kaplan
Meyer Kattan
Mark Kersten
Burton I. Korelitz
Suzanne Kramer
Isadore Kreel
Joel Kreitzer
Leslie Kuhn
Phillip Landrigan
Mark G. Lebwohl
Albert M. Lefkovits
Harold G. Levine
Michael Levitt
Charles S. Lieber
Charles Lockwood
Andrew McElhinney
P. J. McLeod
Charles K. McSherry
Roy Marcus
Lynda Mandell
Robert Matz
Leonard Meiselas
Alter Metzger
Burt R. Meyers
Jasmin Moshipur
Paulo A. Paciucci
Fiorenzo Paronetto
Dimitri Pertsemlidis
Robert Petersdorf
Robert G. Phelps
Robert A. Phillips
C. S. Pitchumoni
Edward Raab
Jacob H. Rand
Elliot J. Rayfield
Allan P. Reed
Rosamond Rhodes
Seymour Rosenblatt
Allan E. Rubenstein
Henry Sacks
Barry Salky
Martin H. Savitz
Fenton Schaffner
Harry Schanzer
Clyde B. Schechter
Robert Scully
Michael J. Serby
Harry Spiera
Charles Spirn
Richard Stein
Barry D. Stimmel
Nelson N. Stone
James J. Strain
Mark Swartz
Louis Teichholz
Moses Tendler
Jaime Uribarri
Samuel Waxman
Lawrence Werther
Jerry A. Winkelstein
Barnett Zumoff

Author, Subject, Title Index to Volume 64

A doctor's perspective, K Hirschhorn: 64(2):105–107
Abdominal access in open and laporascopic surgery, by EKM Tsoi, CH Organ; AJ McElhinney, reviewer: 64(4&5): 356
Acute gouty sacroiliitis: a case report and review of the literature, B Bastani, R Vemuri, M Gennis: 64(6):383–385
Acute meningococcemia, A Sapadin, M Gordon, EJ Bottone: 64(4&5):353
Acute stroke: emergency management and future interventions, D Nassissi: 64(4&5):241–248
Acute treatment of supraventricular tachycardia. MNS Langan: 64(2):142–145
Alagöl F: see Azizlerli H
Alcohol, withdrawal: 64(4&5):249–257
Alcoholism: 64(2):125–129
5 Alpha-Reductase inhibitors: 64(1):20–25
Alzheimer's disease: 64(6):372–375
American cardiology: the history of a specialty and its college, by WB Fye; LA Kuhn, reviewer: 64(6):420
America's ecumenical health policy: a century of consensus, DM Fox: 64(2):72–74
Aminoglycosides: 64(6):386–391
Anemia secondary to low erythropoietin in a patient with normal renal function, AM Kallab, G Dabaghian, T Terjanian: 64(6):406–408
Aneurysm, aorta: 64(4&5):316–322; communicating: 64(3): 217–221
Angioplasty: 64(4&5):258–274
Angle-Closure glaucoma, A Khan: 64(4&5):354
Antibiotics, prophylactic, topical: 64(3):187–188
Anticardiolipin: 64(6):376–382
Antiphospholipid antibody syndrome: an acquired cause of venous and arterial hypercoagulability, M Petri: 64(6):376–382
Aortic dissection: 64(4&5):316–322
Argiris A, Splenic and renal infarctions complicating atrial fibrillation: 64(4&5):342–349
Aromatase inhibitors: 64(1):20–25
Aronson S: see Silvestri S
Arrhythmias and antiarrhythmic drugs, BF Hoffman: 64(2)136–141
Arrhytmias, mechanisms: 64(2):136–141; supraventricular: 64(2):142–145
Arterial occlusion: 64(4&5):316–322
Asthma: 64(4&5):275–282
Asymptomatic hepatopathy is frequent in chronic alcoholic pancreatitis, JMF Chebli, E Lobo, VP Lanzoni, MMD Neves: 64(2):125–129
Ault MJ: see Ng PK
Azizlerli H, Tanakoi R, Terzioğlu T, Alagöl F, Dizdaroglu F, Steroid cell tumor of the ovary as a rare cause of virilization: 64(2):130–135

Basic science contributions of Leonard I. Malis, PW Carmel: 64(3):182–186
Bastani B, Vemuri R, Gennis M, Acute gouty sacroiliitis: a case report and review of the literature: 64(6):383–385
Berman AJ: see Kruger L
Beta-agonists: 64(4&5):275–282
Biorbitofrontobasal interhemispheric approach for suprasellar lesions, K Ohata, A Hakuba, K Nagai, M Morino, Y Iwa; 64(3):217–221
Blam ME, Hammer GS: Extended-interval dosing of aminoglycosides: 64(6):386–391
Blaustein HS, Wysell M, Pulmonary and skeletal tuberculosis: 64(6):419
Book reviews
- *Abdominal access in open and laporascopic surgery,* by EKM Tsoi, CH Organ: 64(4&5):356
- *American cardiology: the history of a specialty and its college,* by WB Fye: 64(6):420
- *Comparative vertebrate neuroanatomy, evolution and adaptation,* by AB Butler, W Hodos: 64(6):425–426
- *Crohn's disease,* by C Prantera, BI Korelitz: 64(4&5): 357–358
- *Disorders of personality: DSM-IV and beyond,* by T Millon with RD Davis: 64(6):427
- *Future practice alternatives in medicine,* by DB Nash: 64(2):147–148
- *Good doctors, good patients, partners in HIV treatment,* by L Sherr, editor: 64(6):421–423
- *Grief and AIDS,* by L Sherr, editor: 64(6):421–423
- *Hives of sickness, public health and epidemics in New York City,* by D Rosner, editor: 64(6):427–428
- *Keep on running: the science of training and performance,* by E Newsholme, T Leech, G Duester: 64(4&5): 356
- *Our health, our lives: a revolutionary approach to total health care for women,* by E Hoffman: 64(4&5):355
- *Patient or pretender: inside the strange world of factitious disorders,* by Feldman MD, Ford CV, with Reinhold T: 64(6):423–424
- *Pharmacology, biology and clinical applications of androgens: Current status and future prospects. Proceedings of the second international androgen workshop, Long Beach, California, February 17–20, 1995,* by S Bhasin, HL Gabelnick, GM Spieler, RS Swerdoff, C Wang, C Kelly, editors: 64(6):429
- *Physicians guide to managed care,* by DB Nash: 64(2): 148–149
- *Textbook on psychiatric epidemiology,* by MT Tsuang, M Tohen, GEP Zehner, editors: 64(6):428–429
- *The handbook of self-concept: developmental, social and clinical considerations,* by BA Bracken, editor: 64(6):426–427
- *Understanding acute low back problems,* by S Bigos, O Bower, G Braen, et al.: 64(2):149
- *What works: reducing re-offending, guidelines from research and practice,* by J Mcguire, editor: 64(6):424–425

Borrelia burgdorferi: 64(6):409–412
Bottone EJ: see Sapadin A
Brisman MH, Camins MB, Radiologic evaluation in patients with head injury: 64(3):226–232
Broselow tape: 64(4&5):302–310
Buchanan A, Distributive justice in health care: 64(2):90–95

Camins MB: see Brisman MH
Can age-based rationing of health care be morally justified?, MM Rivlin: 64(2):113–119
Carmel PW, Basic science contributions of Leonard I. Malis, 64(3):182–186
Castration, medical: 64(1):20–25
Catheter, central venous: 64(4&5):350–352
  peripheral: 64(2):130–135; 64(4&5):350–352
Catholic perspective on access to health care, CJ Fahey: 64(2):80–83
Cerebral, hemisphere, white matter: 64(3):197–206
Cerebral perfusion, pressure: 64(4&5):329–338
Chassin MR, The health care juggling act: balancing universal access, cost containment, and quality improvement; 64(2):101–104
Chebli JMF, Lobo E, Lanzoni VP, Neves MMD, Asymptomatic hepatopathy is frequent in chronic alcoholic pancreatitis. 64(2):125–129
Child abuse: 64(4&5):302–310
Colp Award: 64(4&5):iii
Comparative vertebrate neuroanatomy, evolution and adaptation, by AR Butler, W Hodos: MY McGinnis, reviewer: 64(6):425–426
Connective tissue disease: 64(6):363–371
Contusion, cerebral: 64(3):189–193
Cost containment: 64(2):101–104
Craniopharyngioma: 64(3):217–221
Crohn's disease: 64(1):1–7
Crohn's disease, by C Prantera, BI Korelitz; LS Friedman, reviewer: 64(4&5):357–358
CT scan: 64(3):226–232; 64(6):372–375; abdominal: 64(4&5):311–315
Current trends in onychomycosis therapy: a literature review, D Hecker: 64(6):399–405
Cushing's triad: 64(3):189–193

Dabaghian G: see Kallab AM
Dementia: 64(6):372–375
Dermatology Notes
  Acute meningococcemia: 64(4&5):353
  Iatrogenic Cushing's syndrome: 64(2):146
  Lyme Disease: 64(6):418
  Onychomycosis vs psoriasis: 64(6):417
  Sarcoidosis: 64(1):26
Diabetes: 64(6):406–408
Disaster medicine, NS Oster: 64(4&5):323–328
Disorders of personality: DSM-IV and beyond, by T Millon with RD Davis; R Kirrane, reviewer: 64(6):427
Distributive justice in health care, A Buchanan: 64(2):90–95
Dizdaroglu F: see Azizlerli H
Dosing, once daily: 64(6):386–391
Drug overdose: 64(4&5):249–257
Duodenum: 64(4&5):339–341

Editorial, Savitz MH, Leonard I. Malis, honoris causa: 64(3):153–154
Electrophysiology, cardiac: 64(2):136–141
Emergency airway management, PH Hamilton, JJ Kang: 64(4&5):292–301
Emergency department management of acute myocardial infarction, E Mintz: 64(4&5):258–274
Emergency medicine, theme issue: 64(4&5):239–338
Erythropoietin: 64(6):406–408
Ethics of managed care, F Rosner for the Committee on Bioethical Issues of the Medical Society of the State of New York: 64(1):8–19
Evaluation of blunt abdominal trauma: the evolving role of ultrasound, S Givre, S Kessler: 64(4&5):311–315
Evaluation of seizures in the emergency department, A Jagoda, L Richardson: 64(4&5):249–257
Extended-interval dosing of aminoglycosides, ME Balm, GS Hammer: 64(6):386–391

Fahey JA, Catholic perspective on access to health care: 64(2):80–83
Federal Emergency Medical Assistance: 64(4&5):323–328
Federal Response Program: 64(4&5):323–328
Fibrillation, atrial: 64(4&5):342–349
Fishbein MC: see Ng PK
Fluconazole: 64(6):399–405
Forbes JA, Protestant perspective on access to health care: 64(2):75–79
Fox DM, America's ecumenical health policy: a century of consensus: 64(2):72–74
Friedman LS, reviewer, *Crohn's disease,* by C Prantera, BI Korelitz: 64(4&5):357–358
Fukusumi A: see Huang YP
Future practice alternatives in medicine, by DB Nash: S Reichman, reviewer: 64(2):147–148

Gabrilove JL, reviewer, *Pharmacology, biology and clinical applications of androgens: current status and future prospects. Proceedings of the second international androgen workshop, Long Beach, California, February 17–20, 1995,* by S Bhasin, HL Gabelnick, GM Spieler, RS Swerdoff, C Wang, C Kelly, editors: 64(6):429; see Levine AC
Gennis M: see Bastani B
Gentamycin: 64(6):386–391
Gilbert HS, reviewer, *Our health, our lives: a revolutionary approach to total health care for women,* by E Hoffman: 64(4&5):355
Giorgi DF, Jagoda A, Poisoning and overdose: 64(4&5):283–291
Givre SD, Kessler S, The evaluation of blunt abdominal trauma: the evolving role of ultrasound: 64(4&5):311–315
Globus Award: 64(4&5):iii
Gonadotropin-Releasing hormones, agonists: 64(1):20–25
Good doctors, good patients, partners in HIV treatment, by L Sherr, editor. M Teitelman, reviewer: 64(6):421–423
Goodman B, reviewer, *Patient or pretender: inside the strange world of factitious disorders,* by Feldman MD, Ford CV, with Reinhold T: 64(6);423–424
Gordon M: see Sapadin A
Gout: 64(6):383–385
Grand Rounds
  Acute treatment of supraventricular tachycardia: 64(2): 142–145
  Antiphospholipid antibody syndrome: an acquired cause of venous and arterial hypercoagulability: 64(6):376–382
  Granulomatous disorders: 64(1):1–7
  Silicone breast implants and connective tissue disease: an overview: 64(6):363–371
  Utility of CT scanning in diagnosing dementia: 64(6):372–375
Gribetz D, Pediatrics at Mount Sinai: 64(6):392–398
Grief and AIDS, by L Sherr, editor. M Teitelman, reviewer: 64(6):421–423
Griseofulvin: 64(6):399–405
Gutstein DE, Rosenberg SJ, Nontraumatic intramural hematoma of the duodenum complicating warfarin therapy: 64(4&5):339–341

Haber JG, Putting the care into health care: 64(2):96–100
Hakuba A: see Ohata K
Hamilton PH, Kang JJ, Emergency airway management: 64(4&5):292–301
Hammer GS: see Blam ME
Head injury, closed: 64(3):189–193
Health care, access to: Catholic perspective: 64(2):80–83; Jewish perspective: 64(2):84–89; philosophic perspectives: 64(2):90–100; Protestant perspective: 64(2):75–79; public policy: 64(2):101–111
Health care, aged-based rationing: 64(2):113–119; distributive justice; 64(2):90–95; fairness: 64(2):113–119; managed: 64(1):8–19
Health care juggling act: balanced universal access, cost con-

tainment, and quality improvement, MR Chassin: 64(2):101–104
Hirschhorn K, A doctor's perspective: 64(2):105–107
Hecker D, Current trends in onychomycosis therapy: a literature review: 64(6):399–405; Onychomycosis vs psoriasis: 64(6):417
Hematoma of duodenum: 64(4&5):339–341
Heparin: 64(4&5):258–274
Herman E: see Nadelman RB
Hirschman, SZ, reviewer, *Hives of sickness, public health and epidemics in New York City,* by D Rosner, ed: 64(6):428
Hirudin: 64(4&5):258–274
Hives of sickness, public health and epidemics in New York City, by D Rosner, editor: SZ Hirschman, reviewer: 64(6):427–428
Hoffman BF, Arrhythmias and antiarrhythmic drugs: 64(2):136–141
Holden G: see Rosenberg G
Huang YP, Neuroradiology at The Mount Sinai Hospital: 64(3):194–196
Huang YP, Okudera T, Fukusumi A, Maehara F, Stollman AL, Mosesson R, Lidov M, Mitty HA, Venous architecture of cerebral hemispheric white matter and comments on pathogenesis of medullary venous and other cerebral vascular malformations: 64(3):197–206
Hydrocephalus: 64(3):189–193
Hypercoagulability: 64(6):376–382
Hyperventilation: 64(4&5):329–338

Iatrogenic Cushing's Syndrome, N Schultz, M Lebwohl, 64(2):146
Immunity, cellular: 64(1):1–7
Imperative to heal in traditional Judaism, F Rosner: 64(6):413–416
Infarction, myocardial: 64(4&5):258–274; renal: 64(4&5):342–349; spleen: 64(4&5):342–349
Infection, wound: 64(3):187–193
Injury, head: 64(3):226–232
Intracranial pressure: 64(3):189–193; 64(4&5):329–338
Introduction: issues in emergency medical care and resuscitation, S Jacobson: 64(4&5):239–240
Intubation: 64(4&5):292–301; rapid sequence: 64(4&5):292–301
Issues in medical ethics, religious and philosophic perspectives on access to health care, DA Moros, R Rhodes, A Rochibaud: 64(2):71–111; panel discussion: 108–111: 1997 program: 64(2):112
Itraconazole: 64(6):399–405
Iwa Y: see Ohata K

Jacobson JH, Early days of microsurgery in Vermont: 64(3):160–163
Jacobson S, Introduction: issues in emergency medical care and resuscitation: 64(4&5):239–240
Jagoda A, Richardson L, Evaluation of seizures in the emergency department: 64(4&5):249–257
Jagoda A: see Richardson L; see Giorgi D
James G, Multisystem granulomatous disorders: 64(1):1–7
Jewish perspective on access to health care, Wechsler HJ: 64(2):84–89
Jewish perspective on research/training of newly dead: 64(2):120–124
John E. Moseley, M.D. 1909–1996, JG Rabinowitz: 64(3):233–234
Judaism: 64(2):120–124; 64(6):413–416

Kallab AM, Dabaghian G, Terjanian T, Anemia Secondary to low erythropoietin in a patient with normal renal function: 64(6):406–408
Kapklein MJ, Mahadeo R. Pediatric trauma: 64(4&5):302–310
Kang JJ: see Hamilton PH
Keep on running: the science of training and performance, by E Newsholme, T Leech, G Duester; S Kupfer, reviewer: 64(4&5):356
Kessler S: see Givre S
Ketamines: 64(4&5):275–282
Ketoconazole: 64(6):399–405
Khan A, Angle-Closure glaucoma: 64(4&5):354
Kirrane R, reviewer, *Disorders of personality: DSM-IV and beyond,* by T Millon with RD Davis: 64(6):427
Kirschenbaum A, see Levine AC
Kruger L, Berman AJ, Leonard I. Malis: An appreciation: 64(3):166–171
Kuhn LA, reviewer, *American cardiology: the history of a specialty and its college,* by WB Fye: 64(6):420
Kupfer S, reviewer, *Keep on running: the science of training and performance,* by E Newsholme, T Leech, G Duester: 64(4&5):356
Kurtin S, Lebwohl M, Sarcoidosis: 64(1):26; Lyme disease: 64(6):418
Kushnir SL, reviewer, *Textbook on psychiatric epidemiology,* by MT Tsuang, M Tohen, GEP Zehner, eds.: 64(6):428–429

Langan MNS: Acute treatment of supraventricular tachycardia: 64(2):142–145
Lanzoni VP: see Chebli JMF
Lavage, gastric: 64(4&5):283–291; peritoneal, diagnostic: 64(4&5):311–315
Lebwohl M: see Kurtin S; see Schultz N
Leonard I. Malis: An appreciation, L Kruger, AJ Berman: 64(3):166–171
Leonard I Malis and prophylactic antibiotics, SI Savitz: 64(3):187–188
Levine AC, Kirschenbaum A, Gabrilove JL, The role of sex steroids in the pathogenesis and maintenance of benign prostatic hyperplasia: 64(1):20–25
Lidov M: see Huang YP
Liver diseases, alcoholic: 64(2):125–129
Lobo E: see Chebli JMF
Lupus anticoagulant: 64(6):376–382
Lupus erythematosus: 64(6):376–382
Lyme disease: 64(6):418
Lyme disease, M Lebwohl, S Kurtin: 64(6):418

Maehara F: see Huang YP
Mahadeo R: see Kapklein MJ
Malis JL, Technical contributions of Leonard I. Malis: 64(3):172–181
Malis LI: 64(3):153; 64(3):166–171; 64(3):172–181; 64(3):182–186; 64(3):187–188
Managed care: 64(1):8–19
Management of life-threatening asthma in the emergency department L Richardson, A Jagoda: 64(4&5):275–282
Mannitol: 64(4&5):329–338
Marti A, Early history of neurosurgery in New York: 64(3):155–159
Mass casualty: 64(4&5):323–328
McElhinney AJ, reviewer, *Abdominal access in open and laporascopic surgery,* by EKM Tsoi, CH Organ: 64(4&5):356
McGinnis MY, reviewer, *Comparative vertebrate neuroanatomy, evolution and adaptation,* by AB Butler: 64(6):425–426
Medical ethics, theme issue: 64(2):71–112
Meningioma: 64(3):217–221
Meningitis, acute: 64(4&5):353
Microneurosurgery in suburbia, MH Savitz: 64(3):222–225
Microscope, operating: 64(3):207–212
Microsurgery: 64(3):160–163; 64(3):164–165
Mintz E, Emergency department management of acute myocardial infarction: 64(4&5):258–274
Mitty HA: see Huang YP
Morino M: see Ohata K
Moros DA, Rhodes R, Robichaud A, Issues in medical ethics, religious and philosophic perspectives on access to health care: 64(2):71–111
Moseley JE: 64(3):233–234
Mosesson R: see Huang YP

Mount Sinai Hospital: 64(3):194–196; 64(6):392–398
Multisystem granulomatous disorders, G James: 64(1):1–7

Nadelman RB, Herman E, Wormser GP, Screening for Lyme disease in hospitalized psychiatric patients: prospective serosurvey in an endemic area: 64(6):409–412
Nagai K: see Ohata K
Nassissi D, Acute stroke: emergency management and future interventions: 64(4&5):241–248
Neuromuscular blockade: 64(4&5):292–301
Neuroradiology at The Mount Sinai Hospital, YP Huang: 64(3):194–196
Neurosurgery, early history of in New York: 64(3):155–159
Neves MMD: see Chebli JMF
Ng PK, Ault MJ, Fishbein MC, Stuck catheter: a case study: 64(4&5):350–352
Nontraumatic intramural hematoma of the duodenum complicating warfarin therapy, DE Gutstein, SJ Rosenberg: 64(4&5):339–341

Ohata K, Hakuba A, Nagai K, Morino M, Iwa Y, Biorbitofrontobasal interhemispheric approach for suprasellar lesions: 64(3):217–221
Okudera T: see Huang YP
Onychomycosis: 64(6):399–405
Onychomycosis vs psoriasis, D Hecker: 64(6):417
Operative microphotography: a Malis Legacy, RJ Radna, VP Sachdev: 64(3):207–212
Ophthalmology Notes
  Angle-Closure glaucoma: 64(4&5):354
Oster NS, Disaster medicine: 64(4&5):323–328
Our health, our lives: a revolutionary approach to total health care for women, by E Hoffman; HS Gilbert, reviewer: 64(4&5):355
Ovary, hilus cell tumor, neoplasms, steriod cell tumor: 64(2):130–135

Pancreatitis, chronic, alcoholic: 64(2):125–129
Paris BEC, The utility of CT scanning in diagnosing dementia: 64(6):372–375
Patient or pretender: inside the strange world of factitious disorders, by Feldman MD, Ford CV, with Reinhold T; B Goodman, reviewer: 64(6):423–424
Pediatrics at Mount Sinai, D Gribetz: 64(6):392–398
Pediatric trauma, MJ Kapklein, R Mahadeo: 64(4&5):302–310
Petri M, Antiphospholipid antibody syndrome: an acquired cause of venous and arterial hypercoagulability: 64(6): 376–382
Pharmacology, biology and clinical applications of androgens: current status and future prospects. Proceedings of the second international androgen workshop, Long Beach, California, February 17–20, 1995, by S Bhasin, HL Gabelnick, GM Spieler, RS Swerdoff, C Wang, C Kelly, editors: JL Gabrilove, reviewer: 64(6):429
Photography: 64(3):207–212
Physicians guide to managed care, by DB Nash; F Rosner, reviewer: 64(2):148–149
Pituitary adenoma: 64(3):217–221
Poisoning and overdose, DF Giorgi, A Jagoda: 64(4&5):283–291
Poisoning, antidotes: 64(4&5):283–291; overdose: 64(4&5): 283–291
Prone-Oblique surgical position, RJ Radna, VP Sachdev: 64(3):213–216
Protestant perspective on access to health care, JA Forbes: 64(2):75–79
Psoriasis: 64(6):417
Pulmonary and skeletal tuberculosis, HS Blaustein, M Wysell: 64(6):419
Putting the care into health care, JG Haber: 64(2):96–100

Quality control: 64(2):101–104

Rabinowitz JG, John E. Moseley, M.D. 1909–1996: 64(3):233–234
Radiologic evaluation in patients with head injury, MH Brisman, MB Camins: 64(3):226–232
Radiology Notes
  Pulmonary and skeletal tuberculosis: 64(6):419
Radna RJ, Sachdev VP, Operative microphotography: a Malis legacy: 64(3):207–212
Radna RJ, Sachdev VP, Prone-Oblique surgical position: 64(3):213–216
Religious perspectives on access to health care: 64(2):75–100
Reichman S, reviewer, *Future practice alternatives in medicine,* by DB Nash: 64(2):147–148
Research and/or training on the newly dead: the Jewish perspective, Rosner F: 64(2):120–124
Resuscitation: 64(4&5):302–310
Rhodes R: see Moros DA
Richardson L: see Jagoda A
Richardson L, Jagoda A, Management of life-threatening asthma in the emergency department: 64(4&5):275–282
Rivlin MM, Can age-based rationing of health care be morally justified?: 64(2):113–119
Robichaud A: see Moros DA
Rosenberg G, Holden G, reviewers, *The handbook of self-concept: developmental, social and clinical considerations,* by BA Bracken, editor: 64(6):426–427
Rosenberg SJ: See Gutstein DE
Rosner F, Imperative to heal in traditional Judaism: 64(6):413–416; Research and/or training on the newly dead: the Jewish perspective: 64(2):120–124; The ethics of managed care: 64(1):8–19; Reviewer, *The physicians guide to managed care,* by DB Nash: 64(2):148–149

Sachdev VP: see Radna RJ
Sacroiliitis: 64(6):383–385
Sapadin A, Gordon M, Bottone EJ, Acute meningococcemia: 64(4&5):353
Sarcoidosis, S Kurtin, M Lebwohl: 64(1):26
Savitz MH, Another look at ventriculosubgaleal shunting procedures: 64(3):189–193; Editorial: 64(3):153–154; Microneurosurgery in suburbia: 64(3):222–225; reviewer, *Understanding acute low back problems,* by S Bigos, O Bower, G Braen, et al.: 64(2):149
Savitz SI, Leonard I. Malis and prophylactic antibiotics: 64(3):187–188
Schultz N, Lebwohl M, Iatrogenic Cushing's syndrome: 64(2): 146
Scleroderma: 64(6):363–371
Screening for Lyme disease in hospitalized psychiatric patients: prospective serosurvey in an endemic area, RB Nadelman, E Herman, GP Wormser: 64(6):409–412
Seizures: 64(4&5):249–257; febrile: 64(4&5):249–257
Semashko DC, Vascular emergencies: 64(4&5):316–322
Seminars
  Arrhythmias and antiarrhythmic drugs: 64(2):136–141
Severe head injury: prehospital and emergency department management, S Silvestri, S Aronson: 64(4&5):329–338
Sex hormones: 64(1):20–25
Sex steroids in the pathogenesis and maintenance of benign prostatic hyperplasia, AC Levine, A Kirschenbaum, JL Gabrilove: 64(1):20–25
Silicone Breast Implants. H Spiera, RF Spiera: 64(6):363–371
Silvestri S, Aronson S, Severe head injury: prehospital and emergency department management: 64(4&5):329–338
Spiera H, Spiera RF, Silicone breast implants and connective tissue disease: an overview: 64(6):363–371
Spiera RF: see Spiera H
Splenic and renal infarctions complicating atrial fibrillation, A Argiris: 64(4&5):342–349
Status asthmaticus: 64(4&5):275–282
Status epilepticus: 64(4&5):249–257
Steroid cell tumor of the ovary as a rare cause of virilization, H Azizlerli, R Tanakoi, T Terzioğlu, F Alagöl, F Dizdaroglu: 64(2)130–135

Stollman AL: see Huang YP
Streptokinase: 64(4&5):258–274
Stress management: 64(4&5):323–328
Stroke: 64(4&5):241–248
Stuck catheter: a case study, PK Ng, MJ Ault, MC Fishbein, 64(4&5):350–352
Subarachnoid hemorrhage: 64(4&5):241–248

T-Cells: 64(1):1–7
Tanakoi R: see Azizlerli H
Technical contributions of Leonard I. Malis, JL Malis: 64(3):172–181
Teitelman M, reviewer, *Good doctors, good patients, partners in HIV treatment,* by L Sherr, ed.: 64(6):421–423; *Grief and AIDS,* by L Sherr, ed.: 64(6):421–423
Terbinafine: 64(6):399–405
Terjanian T: see Kallab AM
Terzioğlu T: see Azizlerli H
Textbook on psychiatric epidemiology, by MT Tsuang, M Tohen, GEP Zehner, editors: SL Kushnir, reviewer: 64(6):428–429
The handbook of self-concept: developmental, social and clinical considerations, by BA Bracken, editor: G Rosenberg, G Holden, reviewers: 64(6):426–427
Theme Issues
  Emergency Medicine: 64(4&5):239–338
  Leonard I Malis: An Appreciation: 64(3):153–232
  Medical Ethics: 64(2):71–112
Thromboembolism, systemic: 64(4&5):342–349
Thrombolysis: 64(4&5):258–274
Thrombolytics: 64(4&5):241–248
Tissue plasminogen activator: 64(4&5):258–274
Toxidromes: 64(4&5):283–291
Transient ischemic attacks: 64(4&5):241–248
Tuberculosis: 64(1):1–7; 64(6):419

Ultrasound: 64(4&5):311–315
Understanding acute low back problems, by S Bigos, O Bower, G Braen et al., MH Savitz, reviewer: 64(2):149
Utility of CT scanning in diagnosing dementia, BEC Paris: 64(6):372–375

Vascular, architecture, malformation, radiologic anatomy: 64(3):197–206
Vascular emergencies, DC Semashko: 64(4&5):316–322
Vemuri R: see Bastani B
Venous architecture of cerebral hemispheric white matter and comments on pathogenesis of medullary venous and other cerebral vascular malformations, YP Huang, T Okudera, A Fukusumi, F Maehara, AL Stollman, R Mosesson, M Lidov, HA Mitty: 64(3):197–206
Ventilation, mechanical: 64(4&5):275–282
Ventriculosubgaleal shunting procedures, MH Savitz: 64(3):189–193
Virilization: 64(2):130–135

Wechsler HJ, Jewish perspective on access to health care: 64(2):84–89
Wegener's granulomatosis: 64(1):1–7
What works: reducing re-offending, guidelines from research and practice, by J McGuire, editor: C Winick, reviewer: 64(6):424–425
Whipple's disease: 64(1):1–7
Winick C, reviewer, *What works: reducing re-offending, guidelines from research and practice,* by J McGuire, editor: 64(6):424–425
Wormser GP: see Nadelman RB
Wound, infection: 64(3):187–188
Wysell, M: see Blaustein HS

Yasargil MG, Advent of microsurgery: 64(3):164–165

Information for Authors

THE MOUNT SINAI JOURNAL OF MEDICINE, established in 1934 as *The Journal of the Mount Sinai Hospital,* is a peer-reviewed general medical journal. It is indexed or abstracted in *Index Medicus, Current Contents, Science Citation Index, Hospital Literature Index, International Nursing Index, Excerpta Medica, Chemical Abstracts, Biological Abstracts,* and major databases. Theoretical and basic science articles for the clinician, reviews, reports of clinical or research experience, articles on any subject affecting the practice of medicine, short notes in any specialty, book reviews, letters, and articles by medical students are welcome. The *Journal* generally follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals as revised in 1997 and modified by *The Journal* to conform to the style employed by it. The *Journal* aims at responding to authors of manuscripts within 8 weeks of submission.

Communications. Manuscripts and correspondence should be addressed to: Editor, *The Mount Sinai Journal of Medicine,* The Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, NY 10029-6574. Phone: (212) 241-6108; FAX: (212) 722-6386; e-mail: msjournal@msvax.mssm.edu.

Authorship Responsibility, Financial Disclosure, and Assignment of Copyright. Each author is required to sign (1) the statement on authorship responsibility; (2) the statement on financial disclosure; and (3) either the statement on copyright transfer or (4) the statement indicating that the author is or was a US government federal employee when this work was conducted and prepared for publication. These statements are printed from time to time on a page in the *Journal* entitled "Required Form for Authors" and can be photocopied for use. Copies may also be obtained from *The Journal's* office. Use additional copies of the form if there are more than six authors, and replace with the appropriate number of the author, e.g., 7th, 8th, etc. The signed original form(s) should be submitted with the manuscript.

Manuscript Preparation. Submit manuscripts in triplicate, including three sets of illustrations (see below). **Manuscripts must be typewritten or computer generated, double spaced throughout (including references, legends, and tables),** on one side of 8½ × 11 inch white bond paper with **one inch** margins. Other than the Title Page, the abstract page and each page containing text, legends, or tables should be numbered sequentially in the **top right corner,** and include a heading or header which identifies the last name of the first author in the **top left corner.** Begin a new page for the title page, abstract, initial page of text, references, each table, and legends. A floppy disk, if available, should accompany the manuscript. The label on the disk should specify the name of the first author, the title of the manuscript, how the disk has been formatted, and the word processing system used (DOS, Windows, or Windows 95). PC format is preferred but a high-density formatted Macdisk is acceptable. The text should be in ASCII, Microsoft Word or Wordperfect.

Drugs must be identified by their generic names. Do not use abbreviations on the title or abstract page. Define all abbreviations on first use in the body of the manuscript.

Any material taken directly from other sources must be accompanied by a written statement from both the author and publisher giving permission to *The Journal* for reproducing it. The authors must document in the manuscript that all clinical investigations described in the manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board or its equivalent. The text must indicate that the informed consent of each subject was obtained. If results of experiments on animals are reported in the manuscript, the text must indicate that these studies were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office or its equivalent which supervises such work.

Title Page. The title page must be double spaced, and not numbered. It should indicate (1) title of the article, phrased as concisely as possible; (2) first and last name of each author, middle initials, if any, and not more than two academic degree(s); (3) institutional affiliation and title or rank of each author; (4) name and address of department(s) and institution(s) from which the work originated; (5) the name and address (and voice and FAX telephone numbers if available) of the author who will receive and respond to correspondence; (6) the name and full postal address of the author from whom reprint(s) are to be requested; (7) acknowledgments of sources of grant support; (8) name, place, and date of any conferences at which some or all of the information was presented; and, (9) **a running head of fewer than 40 letter spaces.** At the bottom of the title page, *list 3 to 10 key words or phrases* to facilitate indexing in accord with Medical Subject Headings from Index Medicus. If more than one sheet is needed, label the supplemental sheet as Title Page ii.

Abstract. All articles must include an abstract on the first numbered page of the manuscript of not more than 250 words. Abstracts should be double spaced and divided into four paragraphs:

Background: what problem(s) was(were) addressed;
Methods: how the study was performed;
Results: the salient results;
Conclusions.

Key Words. Three to 10 key words or phrases must be provided at the bottom of the Title Page to facilitate indexing. (see above) Repeat at the end of the Abstract those key words which are listed on the Title Page.

Units of Measurement. SI units are preferred, but values may be expressed in conventional units and conversion factors indicated. The range of normal values for the reporting laboratory must be indicated. When conventional units are used in figures or tables, the appropriate conversion factor(s) must be provided in legends or footnotes.

Editing. All papers will be edited to enhance conciseness and clarity without altering meaning and to ensure conformity with journal style. Authors whose primary language is not English should obtain help from someone proficient in English spelling and grammar.

Illustrations. Photographs, line drawings, and graphs should enhance understanding of the text. Three copies of each must be submitted with the manuscript. Line drawings and graphs should be professionally prepared or computer generated and camera ready. Symbols, lettering, and numbers should be large enough to remain easily legible after the figure has been reduced to fit the width of one column. Photographs must be sharp, high contrast, black and white glossy prints not exceeding 5 inches in height × 7 inches in width. The authors must pay attention to the quality of print reproductions of x-ray plates or transparencies to assure that the special features are labeled and will remain easily visible when reduced to fit the width of one column. The name of the subject and hospital number(s) should not be reproduced in the print. Black and white copies of photomicrographs are preferred and must be cropped to a width of 3⅛ inches. The type of stain and power of magnification must be indicated in the relevant legend. Electron photomicrographs should have internal scale markers. On the back of each print and photograph affix a gum label on which the number of the figure has been written to correspond to its identification in the text, title of manuscript, first author's last name, and the word "top" and arrow to indicate the top edge. **Do not write this information directly on the print and do not mount the print on cardboard.** Illustrations which are to appear together should be mounted accordingly as plates and should be equally sized. Protect the prints by enclosing them in cardboard and separate envelopes. **Do not use paper clips.**

Every effort should be made to avoid using a photograph which includes the face or part of the face of a subject. Facial features should be marked to prevent identification of the subject unless the illustration carries details absolutely essential to the text. **In any case, a partial or full facial photograph of a subject will not be published unless written permission has been obtained from the subject and accompanies the photograph.**

Legends. Legends should not duplicate the text. Each should be on a separate sheet of paper and double spaced. Number each legend to match the illustration it describes. Illustrations mounted as plates to appear together should be accompanied by a single legend identifying the separate elements by position ("upper left," "middle") or by letters. If such illustrations have been labeled with letters, the same letters are to be used in the legend. The legend must indicate the magnification and type of stain used for photomicrographs.

Tables. Each table should be typed on a separate page, double spaced. Number tables consecutively (Table 1, etc.) to correspond to their appearance in the text. Give each table a brief title that is self-explanatory without reference to the text and type the title on a separate line below its number. Identify all abbreviations and/or symbols used in the table in a footnote.

References. All references cited in the text are to be numbered sequentially. Enclose the citation number in parentheses and place it before any punctuation, e.g., **Cytomegalovirus (1), steroids (2,3), and recreational drugs (4–6) have all been implicated (7).** Do not use superscripts. The reference list must be limited to works cited in the text, and numbered in the order in which they are cited. Journal title abbreviations must conform to those used in *Index Medicus.* The styles to be used for various kinds of citations to be listed in the section of the manuscript entitled References are illustrated in the version of "Uniform Requirements" published in the New England Journal of Medicine referenced below. The list of references must be typed, double spaced, on separate pages, following the arrangement and punctuation style as shown in the examples.

1. Brown LK. Sleep apnea syndromes: overview and diagnostic approach. Mt Sinai J Med 1994; 61:99–112.

2. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336(4):309–315.

3. Couser WG. Glomerular diseases. In: Stein J. editor. Internal Medicine. 2nd ed. Boston: Little Brown; 1987. p. 834–861.

List the names of all authors when there are four or fewer. When there are five or more, list the names of the first three, then *et al.*

References to unpublished data (unless the information is In press) and personal communications should not be included in the list of numbered references. Instead, such information should be placed in the text in parentheses. Permission must be obtained from the appropriate individual to so quote the material. This permission must accompany the manuscript at the time of its submission. **If the manuscript is accepted for publication, the author(s) will be asked to confirm the accuracy of all references.**

Proofs. Proofs will be sent to the corresponding author as soon as they are available. Stylistic changes should not be made. Because of increased printing charges, the cost of author's alterations beyond routine correction of typographical errors in text and data will be billed to the author. Proofs should be corrected and returned to and received at the editorial office within 48 hours by express delivery at the author's expense to the address listed above ("Communications").

Offprint Orders. An offprint order form will be sent to the corresponding author with the proofs; if offprints are desired, the form must be returned to the editorial office, preferably with the proofs, but not later than 3 days to avoid late charges. A check for the exact amount in US dollars should be made out to the order of *The Mount Sinai Journal of Medicine.* Please indicate on the check the last name of the first author, and the title of the article. If for one reason or another, the offprint order form is not received with the proofs, it may be obtained directly from the editorial office via telephone or FAX. Offprints are available in minimum quantities of 100, at a cost depending on the number of printed pages and whether covers are desired. The cost of other than routine surface mail delivery, if requested, must be added to the cost of the offprints. Information on the cost of other than routine surface delivery can be obtained from the editorial office.

Required Form for Authors:

AUTHORSHIP RESPONSIBILITY, FINANCIAL DISCLOSURE, AND ASSIGNMENT OF COPYRIGHT

Article Title (type):

Each author must read and sign this form dealing with (1) authorship responsibility, (2) financial disclosure and (3) copyright transfer. An author who was a US federal employee when this work was conducted and prepared for publication, must sign statement (4) instead of statement (3).

1. Authorship Responsibility

I certify that I have participated sufficiently in the conception and design of this work, and the analysis of the data (where applicable), as well as the writing of the manuscript, to take public responsibility for it. I believe that the manuscript represents valid work. I have reviewed the final version of the manuscript and approve it for submission for publication. Neither this manuscript nor one with substantially similar content under my (our) authorship has been published or is being considered for publication elsewhere, except as described in a separate attachment. Furthermore, I agree to produce the original recorded data on which the manuscript is based for examination by the Editor-in-Chief and/or his assignees should such records be requested.

2. Financial Disclosure

I certify that I do not have and have not had an affiliation or financial involvement with or in any organization or entity with a direct financial interest in the subject matter or materials being discussed in the manuscript (eg, employment, consultancies, stock ownership, honoraria), except as disclosed in a separate attachment.

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

3. Copyright

In compliance with the Copyright Revision Act of 1976, the signature of each author on this form shall indicate and be evidence of agreement and mutual understanding with *The Mount Sinai Journal of Medicine*, in consideration of the further action of the *Journal* to review and edit the manuscript being submitted, to transfer, assign, and convey all copyright ownership, including any and all rights incidental thereto, exclusively to *The Mount Sinai Journal of Medicine* if this work is published in the *Journal*.

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

4. US Federal Employees

I was an employee of the US federal government when this work was conducted and prepared for publication; therefore, it is not protected by the Copyright Act and copyright ownership cannot be transferred.

Author(s) Signature(s) **Date**

1st ______________________________

2nd ______________________________

3rd ______________________________

Author(s) Signature(s) **Date**

4th ______________________________

5th ______________________________

6th ______________________________

Return the original signed form to The Editor, The Mount Sinai Journal of Medicine, Mount Sinai School of Medicine, Box 1094, One East 100th Street, New York, N.Y. 10029. Retain one copy of the form for your file. You may make as many photocopies as needed if your manuscript has more than six authors.

THE
MOUNT SINAI JOURNAL OF MEDICINE

Forthcoming:

Grand Rounds

Money, Medicine and Methuselah
Christine K. Cassel
Mount Sinai School of Medicine

The Lactose Permease Meets Frankenstein: New Approaches to Membrane Protein Structure
H. Ronald Kaback
Howard Hughes Medical Institute
University of California
Los Angeles

Elmer's Glue, Elsie and You: Clinical Applications of Adhesion Molecules
Lynn M. Schnapp
Mount Sinai School of Medicine

New Concepts in the Pathogenesis and Treatment of Allergic Asthma
Mitchell H. Grayson and Bruce S. Bochner
Johns Hopkins University
School of Medicine
Baltimore

Theme Issues

Computers in Medicine
Editors: Ray Cornbill and Joseph Kannry

Laparoscopy
Editors: Barry Salky and Michael Edye

Human Immunodeficiency Virus—AIDS
Editor: Henry Sacks

Issues in Hypertension
Editor: Clive Rosendorff

Reproductive Choice: Genetic Counseling and Assisted Reproductive Technology
Editors: Rosamond Rhodes, Daniel A. Moros, Allyson Robichaud

Available now:

Emergency Medicine: Original Articles
Volume 64: Numbers 4&5, 1997: 119 pages. $40.00

Cross-Cultural Issues in Psychopharmacology and Part B: Alumni Theme Issue
Volume 63: Numbers 5&6, 1996: 154 pages. $20.00

MOUNT SINAI
GUSTAVE L.
AND
JANET W.
LEVY
LIBRARY

MOUNT SINAI
GUSTAVE L.
AND
JANET W.
LEVY
LIBRARY

LEVY LIBRARY MT. SINAI MEDICAL CENTER
3 4805 04865529